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Silver Ion-Induced Grob Fragmentation of γ-Amino Iodides: Highly Stereoselective Synthesis of Polysubstituted Piperidines

Guillaume Barbe, Miguel St-Onge, and André B. Charette*

Département de chimie, Université de Montréal, P.O. Box 6128, Station Downtown, Montréal, Québec, Canada H3C 3J7

andre.charette@umontreal.ca

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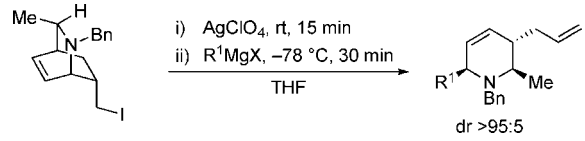
ABSTRACT



A new concerted silver ion-mediated Grob fragmentation process is described in which a 1,2-dihydropyridinium ion is formed and trapped in situ with Grignard reagents in a highly regio- and diastereoselective fashion. Using this methodology, 2,3,6-trisubstituted piperidines were synthesized in good yields and further derivatized to polysubstituted indolizidine.

Piperidines are ubiquitous heterocycles in a growing family of biologically interesting alkaloids. They constitute one of the most common substructures in many natural products[1a] and represent a privileged motif in drug development.[1b] Over the past decades, impressive efforts have been directed toward their preparation[2] and particularly toward the stereoselective synthesis of functionalized polysubstituted nonracemic piperidines.[2c,e] However, the large number of substitution patterns inherently associated with such a saturated heterocycle makes the development of new stereocontrolled routes to polysubstituted piperidines desirable. Herein, we describe a highly diastereoselective synthesis of 2,3,6-trisubstituted piperidines.[3]

As part of our research program directed toward the asymmetric synthesis of substituted piperidines,[4] we recently developed a three-step, multigram-scale stereoselective synthesis of enantiopure aza- bicyclo[2.2.2]octene **1**.[5] Recognizing the fixed antiperiplanar relationship between N−C(γ) and C(α)−C(β) bonds, we envisioned a Grob fragmentation[6] of the corresponding γ-amino halide **2**[7,8] as a precursor of 2,3-dihydropyridinium salt **B** (Scheme 1). The iminium could then be trapped by a nucleophile leading to 2,3,6-trisubsti-

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(2) For recent reviews, see: (a) Buffat, M. G. P. *Tetrahedron* **2004**, *60*, 1701. (b) Weintraub, P. M.; Sabol, J. S.; Kane, J. M.; Borcherding, D. R. *Tetrahedron* **2003**, *59*, 2953. (c) Laschat, S.; Dickner, T. *Synthesis* **2000**, 1781. (d) Mitchinson, A.; Nadin, A.; Ito, Y. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2862. (e) Bailey, P. D.; Millwood, P. A.; Smith, P. D. *Chem. Commun.* **1998**, 633.

(3) For recent examples, see: (a) Garnier, E. C.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2008**, *130*, 7449. (b) Takahashi, M.; Micalizio, G. C. *J. Am. Chem. Soc.* **2007**, *129*, 7514. (c) Wurz, R. P.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 12234. (d) Lemire, A.; Charette, A. B. *Org. Lett.* **2005**, *7*, 2747. For other recent stereoselective synthesis of substituted piperidines, see: (e) Hayashi, Y.; Gotoh, H.; Masui, R.; Ishikawa, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 4012. (f) Sarkar, N.; Banerjee, A.; Nelson, S. G. *J. Am. Chem. Soc.* **2008**, *130*, 9222. (g) Terada, M.; Machioka, K.; Sorimachi, K. *J. Am. Chem. Soc.* **2007**, *129*, 10336. (h) Legault, C.; Charette, A. B. *J. Am. Chem. Soc.* **2005**, *127*, 8966. (i) Weston, M H.; Nakajima, K.; Back, T. G. *J. Org. Chem.* **2008**, *73*, 4630. (j) Amat, M.; Pérez, M.; Minaglia, A. T.; Bosch, J. *J. Org. Chem.* **2008**, *73*, 6920. (k) Davis, F. A.; Xu, H.; Zhang, J. *J. Org. Chem.* **2007**, *72*, 2046.

(4) (a) Larivée, A.; Charette, A. B. *Org. Lett.* **2006**, *8*, 3955, and references therein. (b) Charette, A. B.; Grenon, M.; Lemire, A.; Pourashraf, M.; Martel, J. *J. Am. Chem. Soc.* **2001**, *123*, 11829.

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(6) Grob, C. A. *Angew. Chem., Int. Ed.* **1969**, *8*, 535.

(7) See the Supporting Information for more details.

(8) For the chemoselective reduction of tertiary amides, see: Barbe, G.; Charette, A. B. *J. Am. Chem. Soc.* **2008**, *130*, 18.

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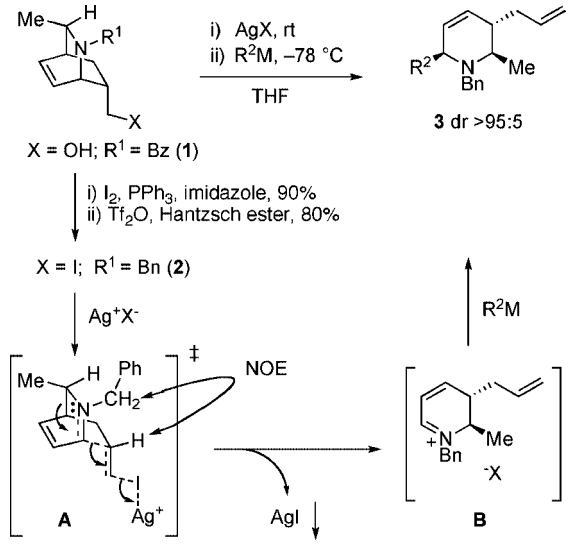
Scheme 1. Synthesis of **2** and Grob Fragmentation Strategy



tuted piperidines such as **3**. The stereoelectronic requirements for frangomeric effect[6] during the fragmentation demand that the nitrogen lone pair be oriented antiperiplanar to the C(β)−C(γ) and C(α)−I bonds. Since the former could be confirmed by NOE experiments,[7] we anticipated the freely rotating C(α)−C(β) bond to allow for proper alignment of orbitals in the hypothetical transition state **A**.[9]

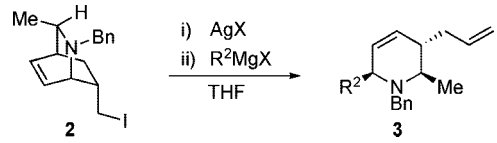
We elected to use the Grignard salt reagent as a versatile family of carbon nucleophiles to trap the iminium. In addition, as **2** was found to be stable at room temperature and to slowly decompose when heated, we elected to perform the fragmentation using silver as halide scavenger. After surveying several silver sources, we were pleased to find that submitting iodide **2** to $AgBF_4$ followed by addition of MeMgBr at room temperature led to a good yield of the desired trisubstituted piperidines (Table 1, entry 7). As is often the case with the α,β-unsaturated iminium, we anticipated regio- and stereocontrol issues. Fortunately, the present conditions yielded the piperidine **3** as a single regio- and diastereomer favoring the 2,6-*cis* relationship (vide infra).

Further improvement of the reaction conditions was executed using $AgClO_4$ (entry 5), a less expensive and more easily handled silver source. After extensive optimization, we found that performing the fragmentation at room temperature and then adding the Grignard at −78 °C provided excellent yields of the corresponding 2,3,6-trisubstituted piperidines **3** with high regio- and diastereoselectivities (entry 13). To our knowledge, this represents the first example of a silver-induced fragmentation of γ-amino halides.[10] Moreover, this *pull*−*push* methodology is a unique and relevant way of applying Grob fragmentation in synthesis and contrasts with the widely used anion-mediated fragmentations (*push*−*pull*).[11]

(9) (a) Zimmerman, H. E.; Weinhold, F. *J. Am. Chem. Soc.* **1994**, *116*, 1579. (b) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon: Oxford, 1983. (c) Hoffmann, R. *Acc. Chem. Res.* **1971**, *4*, 1.

(10) (a) For a recent thermal example, see: Hoffmann, H. M. R.; Frackenpohl, J. *Eur. J. Org. Chem.* **2004**, 4293.

Table 1. Grob Fragmentation−Grignard Addition Optimization

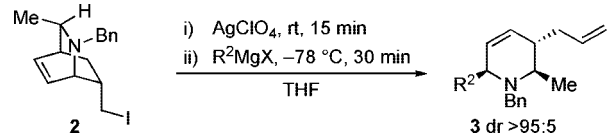


entry	AgX	Ag/Mg (equiv)	T (°C)	rr[c] (%)	dr[c] (%)	yield[c] (%)
1[a]	Ag_3PO_4	2.5/5.0	rt			<5
2[a]	Ag_2SO_4	2.5/5.0	rt			<5
3[a]	Ag_2CO_3	2.5/5.0	rt			5
4[a]	$AgNO_3$	2.5/5.0	rt			7
5[a]	$AgClO_4$	2.5/5.0	rt	<95	<95	76
6[a]	AgOTs	2.5/5.0	rt	<95	<95	81
7[a]	$AgBF_4$	2.5/5.0	rt	<95	<95	85
8[a]	$AgClO_4$	2.5/5.0	−20	<95	<95	<95
9[a]	$AgClO_4$	1.1/5.0	−20	<95	<95	<95
10[a]	$AgClO_4$	1.1/1.5	−20	<95	<95	<95
11[a]	$AgClO_4$	1.1/1.2	−20	<95	<95	94
12[b]	$AgClO_4$	1.1/1.5	−20	93	<95	<95
13[b]	$AgClO_4$	1.1/1.5	−78	<95	<95	93

[a] MeMgBr was used as a nucleophile. [b] *n*-PrMgBr was used as a nucleophile. [c] Determined by ^{1}H NMR.

With our optimal conditions in hand, we evaluated the scope of the reaction. As shown in Table 2, sp^3 (entries 1−5),

Table 2. Synthesis of 2,3,6-Trisubstituted Piperidines[a]



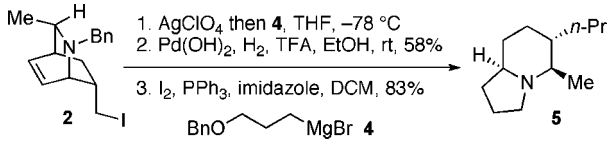
entry	R^2MgX	product	isolated yield (%)
1	Me-MgBr	**3a**	88
2	Me-MgBr	**3a**	86[b]
3	*n*-PrMgCl	**3b**	88
4	*i*-PrMgCl	**3c**	55
5	allylMgBr	**3d**	77
6	vinylMgBr	**3e**	75
7	isoprenylMgBr	**3f**	78
8	PhMgBr	**3g**	82
9	2-furylMgBr[d]	**3h**	88
10	1-pentynylMgBr	**3i**	69
11	TMS-C≡CMgBr[c]	**3j**	74
12	$LiAlH_4$	**3k**	74

[a] All reactions performed on 100 mg of **2**. [b] Reaction performed on a 500 mg scale. [c] Prepared from the terminal alkyne and EtMgBr. [d] Prepared from furan, *n*-BuLi, and $MgBr_2$−Et_2O.

sp^2 (entries 6−8), and sp (entries 9 and 10) hybridized carbon nucleophiles react smoothly with the iminium intermediate producing piperidines **3** in good yields with excellent regio- and diastereoselectivity. Furthermore, using $LiAlH_4$ as a nucleophile afforded the corresponding 1,2,3,6-tetrahydropyridine in 74% yield as a single regioisomer.

The synthetic relevance of this methodology is exemplified in Scheme 2.

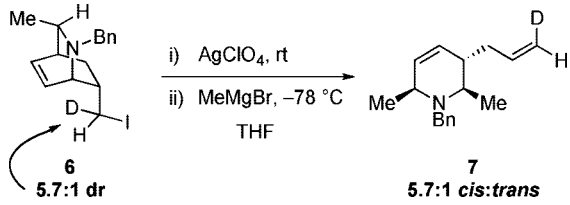
Scheme 2. Stereoselective Synthesis of Indolizidine



A three-step sequence starting with our silver ion-induced fragmentation strategy with Grignard **4** followed by hydrogenation/hydrogenolysis and cyclization produced indolizidine **5** as a single stereoisomer.[12] It is also noteworthy that the absolute stereochemical information is completely retained throughout the course of the reaction.[7,13]

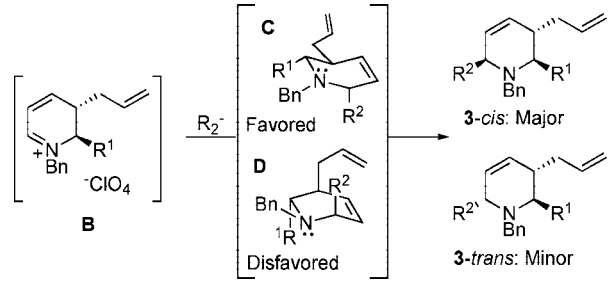
In order to gain mechanistic insights into the Grob fragmentation, we submitted the diastereoenriched iodide **6** to our reaction conditions (Scheme 3).[7] Complete transfer

Scheme 3. Mechanistic Insights



of stereochemical information was observed from the chiral iodide to the terminal alkene (**7**). This is suggestive of a concerted fragmentation mechanism related to transition state **A** (Scheme 1).[14] The 2,6-*cis* relationship of piperidines **3** can be rationalized by considering an axial attack of the Grignard reagent onto the iminium species **B**. The stereoelectronic requirements of such a process leads to two possible boat conformations **C** and **D** with the former being expected to be more stable by positioning both substituents pseudoequatorial (Scheme 4).

Scheme 4. Postulate for the Origin of the Diastereoselectivity



In conclusion, a new concerted silver ion-mediated Grob fragmentation process was described in which a 1,2-dihydropyridinium ion is formed and trapped in situ with Grignard reagents in a highly regio- and diastereoselective fashion. Using this methodology, 2,3,6-trisubstituted piperidines were synthesized in good yields and further derivatized to polysubstituted indolizidine. Efforts are directed at target-oriented synthesis of piperidine-containing natural products, and the results will be reported in due course.

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Supporting Information Available: Experimental details and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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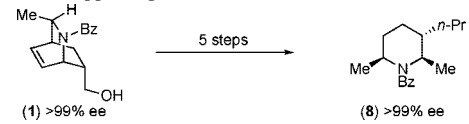
(11) Alkoxide: (a) Wharton, P. S. *J. Org. Chem.* **1961**, *26*, 4781. Boronate: (b) Marshall, J. A.; Bundy, G. L. *J. Am. Chem. Soc.* **1966**, *88*, 4291. Enolate: (c) Brown, J. M.; Cresp, T. M.; Mander, L. N. *J. Org. Chem.* **1977**, *42*, 3984. For recent synthetic applications, see: (d) Larionov, O. V.; Corey, E. J. *J. Am. Chem. Soc.* **2008**, *130*, 2954. (e) Maimoine, T. J.; Voica, A.; Baran, P. S. *Angew. Chem., Int. Ed.* **2008**, *47*, 3054.

(12) Most amines in this paper have been purified using our recently reported, silica gel chromatography free procedures. See refs 7 and 8 for more details.

(13) Enantiomeric purity was determined by SFC using chiral stationary phases. See the Supporting Information for more details.



(14) At the present time, we cannot rule out the formation of a carbocation at C-α followed by a fragmentation that is faster than C−C bond rotation. However, we believe that the formation of a primary carbocation under these conditions is unlikely. For recent calculations, see: Alder, R. W.; Harvey, J. N.; Oakley, M. T. *J. Am. Chem. Soc.* **2002**, *124*, 4960.