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Stereoselective Synthesis of 2,3,6-Trisubstituted Tetrahydropyridines via Tf_2O-Mediated Grob Fragmentation: Access to Indolizidines (−)-209I and (−)-223J

Gérald Lemonnier 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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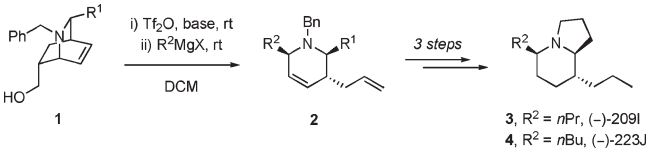
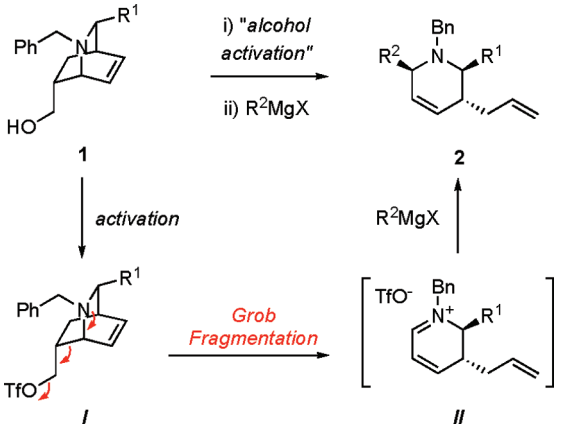


Herein we describe the γ-amino hydroxide Grob fragmentation of the aza-bicyclo[2.2.2]octene **1** using triflic anhydride as the activating agent. The resulting dihydropyridinium ion can react with a wide variety of Grignard reagents, giving access to 2,3,6-trisubstituted tetrahydropyridines (**2**) with high regio- and stereoselectivities. This methodology has been applied to the short synthesis of natural indolizidines (−)-209I (**3**) and (−)-223J (**4**).

Piperidine and indolizidine subunits are found in numerous biologically active natural products[1] and medicinal drugs.[2] For the past 10 years, their synthesis has been widely studied,[3] but stereoselective synthesis of variously substituted rings still remains a contemporary area of research.[4] Recently, as part of our program to develop new stereoselective access to nitrogen-containing heterocycles,[5] our group reported an original synthesis of 2,3,6-trisubstituted dihydropyridines based on a silver ion-induced Grob fragmentation of γ-amino iodides.[5c,6] Since this method displayed high efficiency and stereoselectivity, we were interested in employing it in the synthesis of naturally occurring nitrogen-containing heterocycles. However, this process required the use of a stoichiometric amount of an expensive silver salt. Hence, in this note, we describe our efforts toward the elaboration of a silver-free Grob fragmentation and its application to the enantioselective synthesis of dendrobatid indolizidine alkaloids (−)-209I and (−)-223J.

To overcome the use of the silver salt, we envisioned that the alcohol functionality of the aza-bicyclo[2.2.2]octene **1**[7] could be activated via its corresponding *O*-triflyl intermediate ***I***.[8] A thermal Grob fragmentation could then occur, leading to the dihydropyridinium salt ***II*** that would then be trapped *in situ* by a nucleophile such as a Grignard reagent (Scheme 1).

SCHEME 1. Silver-Free Grob Fragmentation



During the optimization process, using the bicyclo[2.2.2]-octene **1a** (R^1 = Me) as a test substrate, triflic anhydride proved to be the most efficient electrophile for the *in situ* transformation of the alcohol function into a suitable leaving group.[9] To examine the intermediates involved in this

(1) For reviews, see: (a) Daly, J. W.; Spande, T. F.; Garraffo, H. M. *J. Nat. Prod.* **2005**, *68*, 1556. (b) O'Hagan, D. *Nat. Prod. Rep.* **2000**, *17*, 435. (c) Bailey, P. D.; Millwood, P. A.; Smith, P. D. *Chem. Commun.* **1998**, *6*, 633. (d) Michael, J. P. *Nat. Prod. Rep.* **2008**, *25*, 139.

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(3) For recent reviews, see: (a) Escolano, C.; Amat, M.; Bosch, J. *Chem.—Eur. J.* **2006**, *12*, 8198. (b) Cossy, J. *Chem. Rec.* **2005**, *5*, 70. (c) Buffat, M. G. P. *Tetrahedron* **2004**, *60*, 1701. (d) Weintraub, P. M.; Sabol, J. S.; Kane, J. M.; Borcherding, D. R. *Tetrahedron* **2003**, *59*, 2953. (e) Laschat, S.; Dickner, T. *Synthesis* **2000**, 1781. (f) Felpin, F.-X.; Lebreton, J. *Eur. J. Org. Chem.* **2003**, 3693.

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(8) For review on nucleofugality and for examples of fragmentation involving triflate leaving group, see: (a) Lepore, S. D.; Mondal, D. *Tetrahedron* **2007**, *63*, 5103. (b) Murphy, J. A.; Mahesh, M.; McPheators, G.; Anand, R. V.; McGuire, T. M.; Carling, R.; Kennedy, A. R. *Org. Lett.* **2007**, *9*, 3233. (c) Kamijo, S.; Dudley, G. B. *J. Am. Chem. Soc.* **2006**, *128*, 6499.

(9) See Supporting Information for detailed optimization data.

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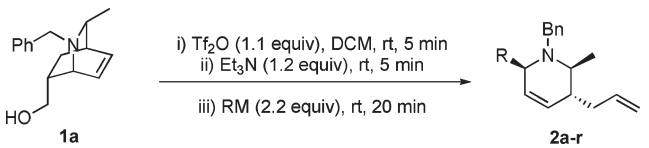
TABLE 1. Scope of the Silver-Free Grob Fragmentation



entry	RM	product	dr[a]	yield (%)
1	MeMgBr	**2a**	> 19:1	92
2	*n*-PrMgCl	**2b**	> 19:1	92
3	*n*-BuMgBr[b]	**2c**	> 19:1	95
4	*n*-OctylMgBr	**2d**	> 19:1	99
5	2-(1,3-dioxan-2-yl)ethylMgBr	**2e**	> 19:1	92
6	*i*-PrMgCl	**2f**	> 19:1	94
7	CpMgCl	**2g**	> 19:1	77
8[c]	CyMgCl	**2h**	> 19:1	78
9	(1,3-dithiane-2-yl)MgBr[d]	**2i**	> 19:1	72
10	(1,3-dithiane-2-phenyl-2-yl)MgBr[d]	**2j**	6.3:1	88
11	allylMgBr	**2k**	> 19:1	91
12	vinylMgBr	**2l**	> 19:1	94
13	phenylMgBr	**2m**	> 19:1	86
14[e]	furylMgBr	**2n**	10:1	77
15	HC≡CMgBr	**2o**	> 19:1	97
16	$C_3H_7C{\equiv}CMgBr$[f]	**2p**	> 19:1	83
17	TMSC≡CMgBr[f]	**2q**	> 19:1	82
18	$LiAlH_4$	**2r**	> 19:1	78

[a]Determined from ^1H NMR of the crude material. [b]Prepared from *n*BuLi and $MgBr_2 \cdot OEt_2$. [c]Grignard reagent was added at −20 °C. [d]Prepared from corresponding dithiane, *n*BuLi and $MgBr_2 \cdot OEt_2$. [e]THF (0.1 N) was added before nucleophile addition. [f]Prepared from corresponding terminal alkynes and EtMgBr.

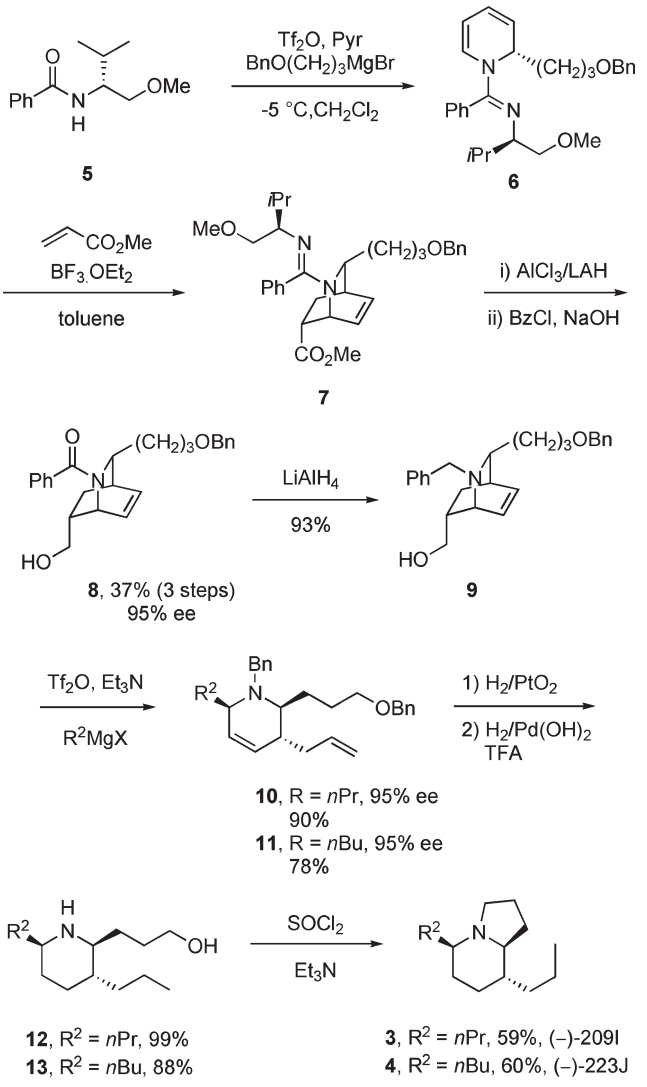
transformation, the fragmentation reaction was performed in deuterated chloroform. The γ-amino alcohol **1a** was dissolved in $CDCl_3$, and 1 equiv of Tf_2O was added. Within 10 min, the formation of the triflate and the subsequent trapping of the triflic acid byproduct by the amine were apparent by ^1H NMR, as indicated by the expected slight shifts of all signals. After the addition of Et_3N, the characteristic allylic signals of the Grob product were immediately observed. This indicates that the γ-amino triflate ***I*** undergoes rapid Grob fragmentation to form the dihydropyridinium salt ***II***.

Our optimized conditions were tested with a wide variety of Grignard reagents, providing an array of substituted tetrahydropyridines in high yields and with high stereoselectivities (Table 1). Primary (entries 1−5 and 11), secondary (entries 6−9), and tertiary (entry 10) sp^3, as well as sp^2 (entries 12−14) and sp (entries 15−17) hybridized carbon nucleophiles are well tolerated in this process. The dihydropyridinium intermediate ***II*** can also be reduced using $LiAlH_4$ (entry 18).

It is noteworthy that unusual Grignard reagents derived from dithiane compounds can be used, even though a moderate selectivity (6.3:1) is obtained for the 2-phenyl-1,3-dithiane magnesium bromide addition (entry 10). Furthermore, in the case of the cyclohexylmagnesium chloride addition (entry 8), the temperature had to be lowered to −20 °C to avoid a β-hydride elimination that would lead to the reduced tetrahydropyridine **2r**.

As depicted in Scheme 2, our strategy has been applied to the expedient stereoselective synthesis of two alkaloids found in poison frog skin: indolizidines (−)-209I and (−)-223J.[10]

SCHEME 2. Synthesis of Indolizidines (−)-209I and (−)-223J



The 1,2-dihydropyridine **6** was prepared as a single regio- and diastereoisomer[11] from valinol derivative **5**, pyridine, and the appropriate Grignard reagent.[12] A subsequent *endo*-selective Diels−Alder condensation gave the bicyclic compound **7**.[7b] In the next step, the amidine and ester functionalities were reduced using aluminum(III) hydride followed by an *in situ N*-benzoylation[7a,13] to give the γ-amido alcohol **8** in 37% overall yield from **5** and with 95% ee.[14] The amide was reduced with $LiAlH_4$ in 93% yield, providing the

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(11) Determined from the crude product, for other examples, see: Charette, A. B.; Grenon, M.; Lemire, A.; Pourashraf, M.; Martel, J. *J. Am. Chem. Soc.* **2001**, *123*, 11829.

(12) Prepared from 1,3-propanediol in a three-step sequence of alcohol monoprotection/bromination/oxidative addition; see: (a) Frankowski, K. J.; Golden, J. E.; Zeng, Y.; Lei, Y.; Aubé, J. *J. Am. Chem. Soc.* **2008**, *130*, 6018. (b) Bode, J. W.; Carreira, E. M. *J. Org. Chem.* **2001**, *66*, 6410. (c) Kende, A. S.; Hernando, J. I. N.; Milbank, J. B. J. *Tetrahedron* **2002**, *58*, 61.

(13) Lemire, A.; Beaudoin, D.; Grenon, M.; Charette, A. B. *J. Org. Chem.* **2005**, *70*, 2368.

(14) Determined by chiral SFC, see Supporting Information.

γ-amino alcohol precursor **9**; the latter underwent fragmentation and subsequent reaction with Grignard reagents, thus producing tetrahydropyridines **10** and **11** in 90% and 78% yield, respectively. SFC analysis on chiral stationary phase indicated that the enantiomeric excess remained unchanged after this transformation. The alkenes were hydrogenated using PtO_2 catalysis under 400 psi of H_2; the use of other metal catalysts, such as $Pd(OH)_2/C$, Rh/C, or Pt/C, resulted in a mixture of the corresponding C_6-epimerized piperidine. The benzyl protecting groups were then removed using catalytic $Pd(OH)_2/C$ and trifluoroacetic acid under 400 psi of H_2. Finally, the resulting piperidines **12** and **13** were converted into the corresponding indolizidines (−)-209I **3** ($[\alpha]^{20}_D = -143.4$ (*c* 0.99, acetone), lit. $[\alpha]^{29}_D = -123.4$ (*c* 0.71, acetone),[10b] $[\alpha]^{24}_D = -126.5$ (*c* 0.19, acetone)[10d]) and (−)-223J **4** ($[\alpha]^{20}_D = -105.0$ (*c* 1.02, acetone), lit. $[\alpha]^{26}_D = -90.5$ (*c* 0.70, acetone)[10b]) through a one-pot chlorination/cyclization procedure[15] with 59% and 60% yield respectively.

In conclusion, we have developed an improved procedure for the synthesis of 2,3,6-trisubstituted dihydropyridines based on the Grob fragmentation of a γ-amino hydroxide containing bicyclo[2.2.2]octene scaffold. We have also characterized by proton, carbon, and two-dimensional NMR analysis the triflate dihydropyridinium intermediate. Finally, this methodology has been applied to an expedient total stereoselective synthesis of two frog skin alkaloids: indolizidines (−)-209I (**3**) and (−)-223J (**4**).

Experimental Section

General Procedure for the Grob Fragmentation. To a solution of **1a** (100 mg, 0.411 mmol) in CH_2Cl_2 (0.1 N) was added triflic anhydride (76 μL, 0.452 mmol, 1.1 equiv), and the reaction mixture was stirred at rt for 5 min. Triethylamine (69 μL, 0.493 mmol, 1.2 equiv) was then added (reaction mixture color turned to red, indicating the formation of the dihydropyridinium intermediate). After 5 min, the Grignard reagent (2.2 equiv) was added dropwise; the reaction was stirred for 20 min at rt and was then quenched by the addition of a saturated aqueous solution of sodium bicarbonate (2 mL). Et_2O (10 mL) was added; the resulting mixture was transferred into a separation funnel. The organic layer was separated, and the aqueous layer was washed with EtOAc. Organic layers were combined, dried over Na_2SO_4, and concentrated under reduced pressure to give a crude residue that was purified by flash chromatography using triethylamine neutralized silica gel (2% EtOAc/hexanes).

(2*S*,3*R*,6*R*)-3-Allyl-1-benzyl-6-butyl-2-methyl-1,2,3,6-tetrahydropyridine (2c): 95% yield; yellowish oil; R_f (10% EtOAc/hexanes) = 0.55; ^{1}H NMR ($CDCl_3$, 400 MHz), δ 7.39 (d, *J* = 7.4 Hz, 2H), 7.31 (t, *J* = 7.4 Hz, 2H), 7.22 (t, *J* = 7.3 Hz, 1H), 5.80−5.67 (m, 3H), 4.99−4.87 (m, 2H), 3.80 (s, 2H), 3.23−3.15 (m, 1H), 2.75 (dq, *J* = 4.7, 6.6 Hz, 1H), 2.29−2.20 (m, 1H), 2.14−2.05 (m, 1H), 1.98−1.91 (m, 1H), 1.76−1.65 (m, 1H), 1.41−1.10 (m, 5H), 1.06 (d, *J* = 6.6 Hz, 3H), 0.86 (t, *J* = 7.1, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz), δ 141.9 (C), 137.2 (CH), 129.2 (CH), 128.5 (2xCH), 128.1 (2 × CH), 127.5 (CH), 126.5 (CH), 116.0 (CH_2), 59.3 (CH), 55.4 (CH), 54.5 (CH_2), 41.3 (CH), 38.4 (CH_2), 32.6 (CH_2), 29.2 (CH_2), 23.1 (CH_2), 18.2 (CH_3), 14.2 (CH_3); FTIR (cm^{-1}) (neat) 3746, 2929, 909, 726, 696; HRMS (ESI, Pos) calcd for $C_{20}H_{30}N$ $[M + H]^+$: 284.2373, found 284.2378.

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

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