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Highly Regioselective Transformation of Alkenyl Bromides into α-Bromoaziridines and α-Bromohydrazones

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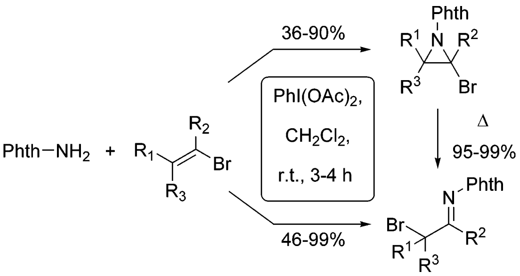
ABSTRACT



The synthetic utility of α-halohydrazones is an underexplored area due to the lack of chemo- and regioselective routes towards these molecules. Herein, we describe a general method for α-bromohydrazone synthesis via the rearrangement of α-bromoaziridines, which can be readily prepared for the first time from the corresponding alkenyl bromides. The rearrangement of α-bromoaziridines into α-bromohydrazones proceeds with high yields and with high selectivities.

α-Halogenated imines and hydrazones have been used for the preparation of diimines,[1] epoxyimines,[2] cyclopropylamines,[3] pyrrolidines,[4] and pyrroles.[1a,5] However, the efficient synthesis of α-halogenated imines and hydrazones[6] is an underdeveloped area in comparison with α-halogenated aldehydes and ketones.[7] This is due to the difficulties encountered during the preparation of these intermediates. The most common methods of α-haloimine or α-halohydrazone synthesis are α-halogenation of imines or hydrazones and condensation of α-halogenated carbonyl compounds with primary amines hydrazines. The condensation pathway proceeds with low chemoselectivity, plagued by side-reactions such as nucleophilic substitution of α-halogen, base-promoted elimination of hydrogen halide, Favorskii rearrangement, and formation of epoxide intermediates.[8] In turn, imine and hydrazone halogenation suffers from poor regio- and chemoselectivity, affording mixtures of mono- and dihalogenated compounds.[8] Herein, we report a novel route to α-bromoaziridines **2** and their rearrangement into α-bromohydrazones **3** (Scheme 1). The electrocyclic nature of the rearrangement allows for a highly regioselective transposition of the halogen atom and control over the product structure.

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[1] (a) Duhamel, P.; Duhamel, L.; Valnot, J. Y. *Tetrahedron Lett.* **1973**, *14*, 1339−1342. (b) De Kimpe, N.; Yao, Z. P.; Schamp, N. *Tetrahedron Lett.* **1986**, *27*, 1707−1710.

[2] Sulmon, P.; De Kimpe, N.; Schamp, N.; Declercq, J. P.; Tinant, B. *J. Org. Chem.* **1988**, *53*, 4457−4462.

[3] De Kimpe, N.; Tehrani, K. A.; Fonck, G. *J. Org. Chem.* **1996**, *61*, 6500−6503.

[4] De Kimpe, N.; Palamareva, M.; Sulmon, P.; Verhe, R.; De Buyck, L.; Schamp, N.; Declercq, J. P.; Tinant, B.; Van Meerssche, M. *Tetrahedron* **1986**, *42*, 71−80.

[5] Duhamel, L.; Valnot, J. Y. *Tetrahedron Lett.* **1974**, *15*, 3167−3170.

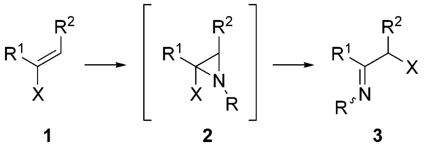
[6] Levkovskaya, G. G.; Drozdova, T. I.; Rozentsveig, I. B.; Mirskova, A. N. *Russ. Chem. Rev. (Engl. Transl.)* **1999**, *68*, 581−604.

[7] Eicher, T.; Hauptmann, S. *The Chemistry of Heterocycles*; Wiley-VCH: Weinheim, Germany, 2003.

[8] De Kimpe, N.; Schamp, N. *Org. Prep. Proced. Int.* **1979**, *11*, 115−199 and references therein.

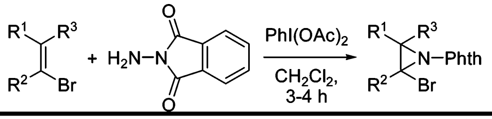
10.1021/ol060336z CCC: $33.50

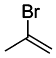
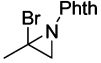
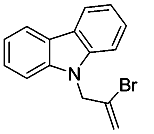
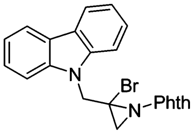
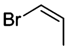
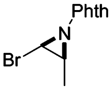
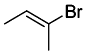
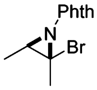
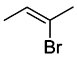
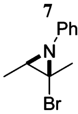
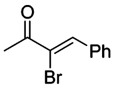
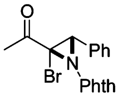
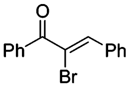
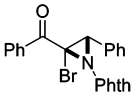
Scheme 1



Literature precedents of haloaziridine chemistry have been limited to the synthesis and reactivity of 2,2-dichloroaziridines.[9] Several reports describe the synthesis of monochlorinated aziridines via reductive dechlorination of 2,2-dichloroaziridines.[10] The addition of chloro- and bromocarbenes to imines is of less preparative value.[11] Rearrangement of di- and polyhalogenated aziridines into the corresponding α-haloimines has been reported.[12] Rearrangements of 2,2-dichloroaziridines followed by the hydrolysis of the intermediate α-chloro imidoyl chlorides result in the formation of amides.[13] At the outset, we sought to develop a general method for bromoaziridine synthesis with the goal of further exploring the chemistry of these molecules. α-Halogenated olefins are not suitable for aziridination using nitrene transfer protocols under typical conditions that involve olefin, chloramine-T, or *N*-tosyl-iminophenyliodinane in the presence of a metal catalyst. Our attempts to obtain monohalogenated aziridines using a range of metal-mediated nitrene transfer reagents to the corresponding olefins have been consistently unsuccessful. Regardless of their origin, the nitrenoid species have not been reactive enough to aziridinate alkenyl bromides. The *N*-aminophthalimide/(diacetoxyiodo)benzene (DIB) system, recently described by us and others, is versatile with regard to the electronic nature of the olefin.[14] To our delight, the nitrenoid species generated from *N*-aminophthalimide using this metal-free protocol has led to a successful aziridination of *E*-2-bromo-but-2-ene to give aziridine **7** as a stable crystalline product in 90% yield. Other commercially available brominated olefins were subjected to the reaction conditions. 3-Bromo-4-phenyl-3-butene-2-one and 2-bromo-1,3-diphenylpropenone were obtained from chalcones via a bromination−dehydrobromination sequence.[15] 9-(2-Bromoallyl)-9*H*-carbazole was synthesized from carbazole via the nucleophilic substitution of 2,3-dibromopropene.[16] The results of aziridination are summarized in Table 1. In the case of 2-bromopropene, 9-(2-bromoallyl)-9*H*-carbazole, 1-bromo-propene, and α-bromo chalcones (entries 1−3, 6 and 7, Table 1), α-bromoaziridines were the only products isolated. The aziridine **4** exists as a mixture of invertomers in a 60:40 ratio, as determined by ^{1}H NMR. *E*- and *Z*-2-bromobut-2-enes predominantly led to aziridines **7** and **8**, containing small amounts of hydrazones (5−10%). All aziridines have been stored at −30 °C to avoid decomposition. However, recrystallized **9** can be stored at room temperature over several months without any signs of degradation. In contrast to α-bromo-substituted *E*-chalcones, which give aziridines in good yields, α-bromo-substituted *Z*-chalcones **11** and **12** led to complicated mixtures of products. Substrates **13** and **14** were found to decompose under the aziridination conditions (Figure 1).

Table 1. Preparation of α-Bromoaziridines



entry	substrate	product	yield, %
1		 **4**	55[a]
2		 **5**	36[b]
3		 **6**	60
4		 **7**	90[c]
5		 **8**	73[d]
6		 **9**	79
7		 **10**	61

[a] Mixture of invertomers in a 60:40 ratio (determined by ^{1}H NMR). [b] 57% conversion. [c] 10% hydrazone was isolated. [d] 5% hydrazone was isolated.

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(9) (a) Fields, E. K.; Sandri, J. M. *Chem. Ind. (London)* **1959**, 1216. (b) Cook, A. G.; Fields, E. K. *J. Org. Chem.* **1962**, *27*, 3686−3687. (c) Senõ, M.; Shiraishi, S.; Suzuki, Y.; Asahara, T. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 1413−1417. (d) Mihara, M.; Komatsu, M.; Ishino, Y.; Minakata, S. *J. Org. Chem.* **2005**, *70*, 5320−5322.

(10) (a) Khlebnikov, A. F.; Kostikov, R. R.; Shklyaev, V. S.; Aleksandrov, B. B.; Dormidontov, M. Y. *Khim. Geterotsikl. Soedin.* **1990**, *8*, 1086−1091. (b) Takahashi, M.; Takada, T.; Sakagami, T. *J. Heterocycl. Chem.* **1987**, *24*, 797−799. (c) Yamanaka, H.; Kikui, J.; Teramura, K.; Ando, T. *J. Org. Chem.* **1976**, *41*, 3794−3797.

(11) (a) Deyrup, J. A.; Greenwald, R. B. *J. Am. Chem. Soc.* **1965**, *87*, 4538−4545. (b) Deyrup, J. A.; Greenwald, R. B. *Tetrahedron Lett.* **1965**, *6*, 321−324.

(12) (a) Anderson, D. J.; Gilchrist, T. L.; Horwell, D. C.; Rees, C. W. *J. Chem. Soc. C* **1970**, *4*, 576−579. (b) Petrov, V. A. *J. Fluorine Chem.* **2000**, *106*, 25−34.

(13) (a) Abou-Gharbia, M. A.; Doukas, P. H. *Heterocycles* **1979**, *12*, 637−640. (b) Petrov, O. S.; Ognyanov, V. I.; Mollov, N. M. *Synthesis* **1987**, *7*, 637−638.

(14) (a) Li, J.; Liang, J.-L.; Chan, P. W. H.; Che, C.-M. *Tetrahedron Lett.* **2004**, *45*, 2685−2688. (b) Krasnova, L. B.; Hili, R. M.; Chernoloz, O. V.; Yudin, A. K. *ARKIVOC* **2005**, *4*, 26−38.

(15) Kowalski, C. J.; Weber, A. E.; Fields, K. W. *J. Org. Chem.* **1982**, *47*, 5088−5093.

(16) Cuvigny, T.; Normant, H. *J. Organomet. Chem.* **1963**, *1*, 120−137.

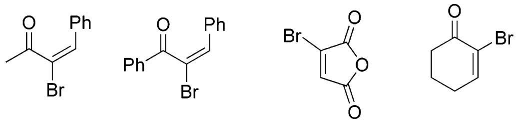
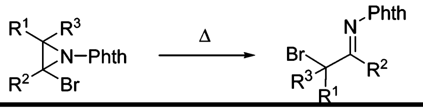
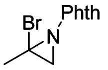
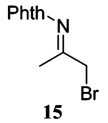
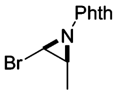
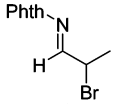
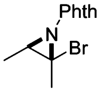
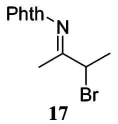
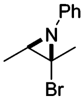
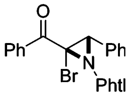
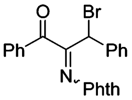

11 12 13 14

Figure 1.

The α-bromoaziridines are thermally labile and undergo a clean rearrangement into the corresponding hydrazones. The conditions required to achieve full conversion are summarized in Table 2. Hydrazones of high purity can be obtained by evaporation of the reaction solvent and purification by crystallization from a hexanes−ethyl acetate mixture. The aziridine **4**, derived from a monosubstituted olefin, requires microwave irradiation to reach completion in a reasonable time. The aziridine **5** decomposed upon heating without the formation of hydrazone.

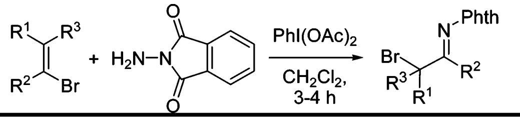
Table 2. Thermal Rearrangement of α-Bromoaziridines

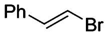
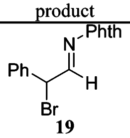
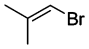
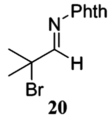
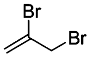
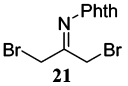


entry	substrate	conditions	yield, %	product
1	 **4**	$CHCl_3$, MW, 150 °C, 10 min	quant	 **15**
2	 **6**	CH_3CN, MW, 130 °C, 10 min	quant	 **16**
3	 **7**	Toluene, 80 °C, 17 h *or* CH_3CN, 50 °C, 15 h	quant	 **17**
4	 **8**	Toluene, 100 °C, 6 days *or* CH_3CN, 50 °C, 15 h	quant	
5	 **10**	Toluene, 50 °C, 24 h *or* CH_3CN, 50 °C, 8 h	95	 **18**

The facility of rearrangement correlates with the stability of the intermediate carbocation. The polar solvents facilitate the ionization process. β-Bromostyrene, 1-bromo-2-methylpropene, and 2,3-dibromopropene, which are progenitors of particularly stable carbocations, proceed directly to hydrazones upon exposure to *N*-aminophthalimide/DIB (Table 3). Aziridine intermediacy can only be implicated in these cases. The crystalline products **19** and **20** are stable compounds, whereas hydrazone **21** was found to decompose over several days even at 0 °C.

Table 3. Aziridination of α-Bromo-Substituted Olefins and Their Rearrangement into Hydrazones



entry	substrate	product	yield, %
1		 **19**	99
2		 **20**	83
3		 **21**	46

Halogenated cyclopropanes,[17] epoxides,[18] or thiiranes are known[19] to rearrange via an electrocyclic mechanism. Their ring openings proceed in a disrotatory manner, and significant torque selectivity can sometimes be observed.[20]

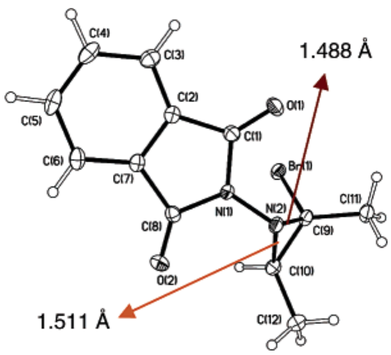


Figure 2. X-ray crystal structure of aziridine **7**.

The X-ray structure of aziridine **7** reveals the $C_{10}-N_2$ bond elongated by 0.023 Å compared to the C_9-N_2 bond, suggesting the relative weakness of the former (Figure 2). During the reaction, transition-state stabilization would likely occur upon partial overlap between the electron density accumulated at the nitrogen of the $C_{10}-N_2$ bond undergoing scission and the σ^* of the C−Br bond (Scheme 2). For

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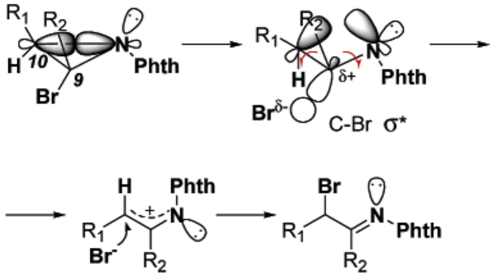
(17) (a) Fields, R.; Haszeldine, R. N.; Peter, D. *J. Chem. Soc. C* **1969**, *1*, 165−172. (b) Baird, M. S.; Lindsay, D. G.; Reese, C. B. *J. Chem. Soc. C* **1969**, *8*, 1173−1178. (c) Werstiuk, N. H.; Roy, C. D. *Tetrahedron Lett.* **2001**, *42*, 3255−3258.

(18) (a) McDonald, R. N.; Tabor, T. *J. Org. Chem.* **1968**, *33*, 2934−2941. (b) Köbrich, G.; Werner, W. *Tetrahedron Lett.* **1969**, *10*, 2181−2183. (c) Gralak, J.; Valnot, J.-Y. *Org. Prep. Proced. Int.* **1979**, *11*, 107−110.

(19) Schoenberg, A.; Knoefel, W.; Frese, E.; Praefcke, K. *Tetrahedron Lett.* **1968**, *9*, 2487−2492.

(20) Woodward, R. B.; Hoffman, R. *J. Am. Chem. Soc.* **1965**, *87*, 3348−3357.

Scheme 2



stereoelectronic reasons, the substituents anti to the leaving group rotate outward as the ionization of the C−Br bond takes place. The addition of Br$^-$ to the aza-allyl cation gives the rearranged product of defined regiochemistry. The lifetime of the formed aza-allyl cation is quite short. For example, attempts to trap the aza-allyl cation with added nucleophiles such as AcO$^-$ and I$^-$, added in situ, were unsuccessful.[21] The addition of excess KOAc/18-crown-6 or Bu_4NI to the aziridination mixture in the case of 1-bromo-2-methylpropene gave only α-bromo hydrazone **20** in reduced yield. Neither acetoxy nor iodo derivatives have been detected.

To summarize, the *N*-aminophthalimide/DIB combination is the method of choice for transforming readily available bromo-olefins into the corresponding aziridines. The resulting products undergo clean thermal rearrangement into α-bromohydrazones. The regioselectivity of bromide migration and the wide availability of brominated olefins allow for excellent control over the site of substitution if a particular substituted product is desired. Other useful reactions of α-haloaziridines,[22] particularly halogen/metal exchange,[23] transition-metal catalyzed reactions, and transformation into azirines, can now be investigated with this straightforward method in hand.

Acknowledgment. We thank NSERC, CFI, ORDCF, ACS-PRF, Amgen, and the University of Toronto for financial support.

Supporting Information Available: The experimental procedures and characterizations of compounds **4**−**10** and **15**−**21** and the X-ray crystal structure of **7** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

OL060336Z

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(21) A reviewer suggested the possibility of intramolecular bromide migration.

(22) *Aziridines and Epoxides in Organic Synthesis*; Yudin, A. K., Ed.; Wiley-VCH: Weinheim, Germany, 2006.

(23) For recent examples of generating magnesiated aziridines from sulfinylaziridines, see: (a) Satoh, T.; Matsue, R.; Fujii, T.; Morikawa, S. *Tetrahedron* **2001**, *57*, 3891−3898. (b) Satoh, T.; Sato, T.; Oohara, T.; Yamakawa, K. *J. Org. Chem.* **1989**, *54*, 3973−3978.