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Published on Web 07/12/2006

A General Process for the Haloamidation of Olefins. Scope and Mechanism

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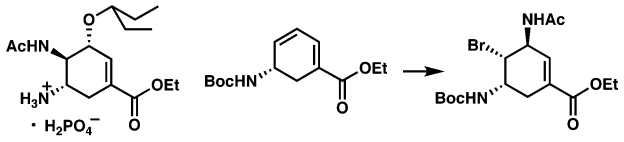
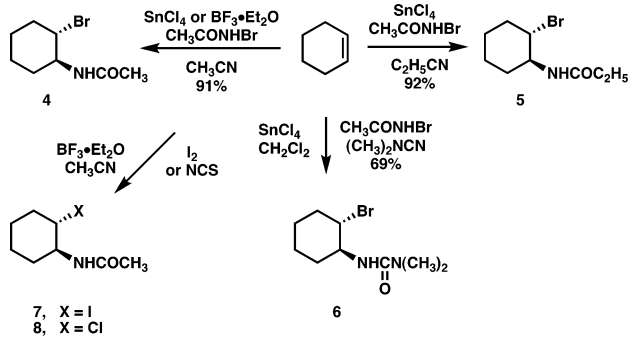
An important step in a recently described synthesis of the antiflu medicine oseltamivir (**1**, Tamiflu) was the bromoamidation of the diene ester **2** to form the bromoamide derivative **3** regio- and stereoselectively.[1] The ready availability of **2** by a short enantioselective synthesis coupled with the effectiveness of the bromoamidation process was critical to the development of this short and efficient (>30% overall yield) route to **1**. In this paper, we provide further evidence of the utility of this haloamidation reaction and information regarding scope and mechanism. The results obtained in this study can serve to guide the rational use of this process for the elaboration of the core C═C functional group to a wide variety of products having the amino function attached at one terminus.

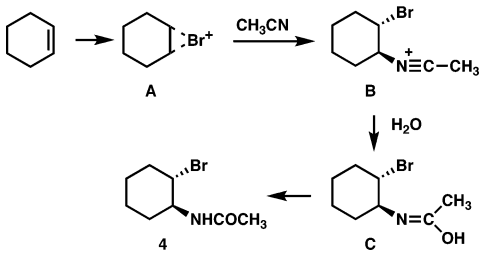


An initial study of bromoamidation was conducted with *N*-bromoacetamide as the halogen source, acetonitrile as solvent, cyclohexene as the olefinic substrate, and $SnCl_4$ as the activating Lewis acid. The previous work had established the superiority of CH_3CN in bromoamidation and the requirement of a Lewis acid to activate the Br^+ donor.[1] Although the use of commercial reagent grade CH_3CN proved to be satisfactory in these initial studies, our more recent experiments have demonstrated that the presence of ca. 1 equiv of water in the reaction mixture is essential for optimum yields. This fact and the observation that CH_3CN was by far the most efficacious solvent for the bromoamidation of olefins suggested that CH_3CN might participate in the reaction by nucleophilic attack on an initial bromonium ion, in a fashion analogous to the well-known Ritter reaction.[2,3] Thus, reaction of cyclohexene, 1.2 equiv of *N*-bromoacetamide, 0.4 equiv of $SnCl_4$, and 1.2 equiv of H_2O in CH_3CN as solvent at 0 °C for 1 h produced the *trans* bromoacetamide **4** stereoselectively in 91% yield, whereas the same reaction in C_2H_5CN as solvent afforded the *trans* bromopropionamide **5** in 92% yield (see Scheme 1). Boron trifluoride etherate ($BF_3{\cdot}Et_2O$) worked just as well as a catalyst for the conversion of cyclohexene to **4** (91% yield) under the same conditions that were used for $SnCl_4$. The *trans* bromo urea derivative **6** was similarly obtained from cyclohexene with *N*,*N*-dimethyl cyanamide (5 equiv) as nucleophile (Scheme 1) in CH_2Cl_2 as solvent. Comparable results were obtained for the bromoamidation of cyclohexene using *N*-bromosuccinimide as Br^+ donor instead of *N*-bromoacetamide, but the process was somewhat more convenient with the latter because the co-product acetamide is water soluble and more easily removed than is succinimide. Treatment of cyclohexene with I_2 using 1 equiv of $SnCl_4$ as catalyst in CH_3CN with 1.2 equiv of H_2O at 23 °C for 1 h gave the iodoacetamide derivative **7** (Scheme 1) in 98% yield. The corresponding reaction with *N*-chlorosuccinimide (NCS) under the same conditions gave a 90% yield of the

Scheme 1. Haloamidation of Cyclohexene



chloroacetamide **8**, but the reaction was slower and required 20 h. The transformations outlined in Scheme 1 show that the amidation process can function to give vicinal iodo-, bromo-, or chloroamides in good yields, and that the reaction pathway from cyclohexene to **4** traverses the intermediates **A**, **B**, and **C**.

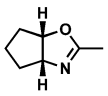
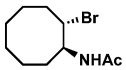
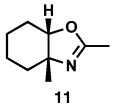
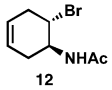
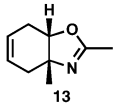
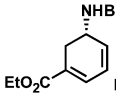
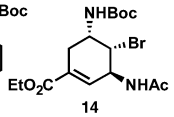
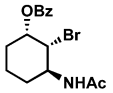
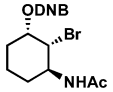
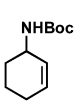
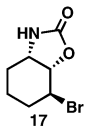
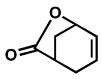
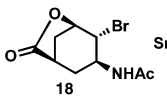
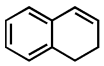
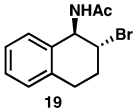


The scope of the bromoamidation process using *N*-bromoacetamide in CH_3CN as solvent is indicated by the 11 examples listed in Table 1. In the case of entry 1, the higher reactivity of the intermediate *trans* bromoamide resulted in further conversion to the oxazoline to produce the oxazoline **9**, which was isolated in 75% yield. A similar result is documented in entries 3 and 5; the intermediate in each case is a reactive *trans* 2-acetamido bromide (isolable by rapid workup) that gives rise to the oxazolines **11** and **13**. The formation of these oxazolines, precursors of the corresponding *cis* amino alcohols, shows that the bromoamidation reaction can be extended to constitute an olefinic amino hydroxylation process.

The examples given in entries 6−10 of Table 1 illustrate a very useful selectivity aspect of the olefinic bromoamidation process apart from the positional selectivity (Markovnikov-type) implied by the cases shown in entries 3 and 5 for trisubstituted olefinic substrates. The example in entry 6 is taken from the original bromoamidation reaction that was employed in our recent synthesis of oseltamivir (**1**). We rationalize the regio- and stereoselectivity of the process by which **14** is formed as follows: (1) bromonium ion complexation *cis* to the NHBoc group is favored by an attractive interaction between the carbonyl oxygen of the Boc group (axially located) and Br^+; (2) preferential diaxial opening by CH_3CN as

10.1021/ja063675w CCC: $33.50

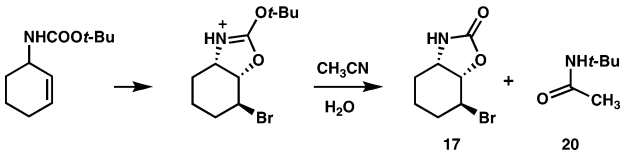
Table 1. Amidation of Olefins at 0 °C[a]

entry	substrate	product	catalyst (eq)	time (h), yield (%)
1		 **9**	$SnCl_4$ (0.4)	1, 75
			BF_3-Et_2O (0.4)	1, 76
2		 **10**	$SnCl_4$ (0.4)	1, 85
3		 **11**	$SnCl_4$ (0.4)	0.5, 70
4		 **12**	$SnCl_4$ (0.4)	1, 40
			BF_3-Et_2O (1.0)	1, 88
5		 **13**	$SnCl_4$ (0.4)	1, 86
6		 **14**	$SnBr_4$ (0.05)	4, 75[b]
			$SnCl_4$ (0.1)	8, 69[b]
7		 **15**	$SnCl_4$ (0.4)	0.5, 74
8		 **16**	$SnCl_4$ (0.4)	1, 72
	DNB = 3,5-dinitrobenzoyl			
9		 **17**	$SnCl_4$ (0.1)	0.5, 90
10		 **18**	$SnCl_4$ (0.4)	2, 81
11		 **19**	BF_3-Et_2O (1.0)	1, 82

[a] Reactions carried with $CH_3CONHBr$ in CH_3CN with 1.2 equiv of H_2O. [b] Reaction temperature was −40 °C.

the nucleophile (on the flipped conformer with equatorial NHBoc) determines both the structure and stereochemistry of product **14**. An exactly analogous argument explains the selective formation of bromoamides **15** and **16** in entries 7 and 8 of Table 1. The structures of **15** and **16** were determined from ^{1}H NMR (400 MHz) spectral analysis of these compounds and their N-deuterated analogues. Structure **17** followed from analysis of the ^{1}H NMR spectral data and also from single-crystal X-ray diffraction analysis. A reasonable pathway for the formation of **17** is shown in Scheme 2. The co-product **20**, which was shown to be present in the crude reaction product by ^{1}H NMR analysis, is readily separated from **17** by hexane extraction, even though the chromatographic mobilities of **17** and **20** are very similar on silica gel.

Scheme 2. Possible Pathway for the Formation of **17** and **20**



17 **20**

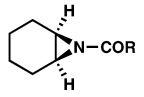
The bromoamidation of the unsaturated bridged γ-lactone in entry 10 of Table 1 involves Br^+ attachment at the sterically less screened face of the double bond and diaxial nucleophilic opening of the resulting bromonium ion to form **18**, the structure of which was confirmed by X-ray crystallographic analysis. The six-membered carbocyclic ring of **18** adopts the boat conformation in the solid state.

The scope of the bromoamidation disclosed herein appears to be quite broad not only with regard to the olefinic component but also in terms of the nitrile partner. A variety of nitriles were found to react with cyclohexene as the test olefin and *N*-bromoacetamide to form the corresponding *trans*-1-bromo-2-acylaminocyclohexanes **21** in the yields indicated below. The reactions were generally carried out in CH_2Cl_2 at 0 °C with 0.4 equiv of $BF_3{\cdot}Et_2O$ as catalyst and 1.2 equiv of water using ca. 15 equiv of the nitrile. In the case of benzonitrile, the reaction was run neat.

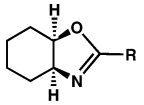
21

R = *t*-Bu (75%)
R = C_6H_5 (77%)
R = CH_2=CH (70%)
R = CH_2CN (61%)
R = CH_2Cl (75%)

The readily available bromoamides **21** also provide access to either *N*-acyl aziridines or oxazolines and a host of other compounds, such as *vic* amino alcohols (from oxazolines by reduction and hydrolysis) or *trans*-β-substituted amines (via ring opening of *N*-acyl aziridines). For example, bromoamides **21**, R = *t*-Bu and C_6H_5, were converted either to *N*-acyl aziridines **22**, R = *t*-Bu (82%) and **22**, R = C_6H_5 (91%), by treatment with 1.2 equiv of LiN($SiMe_3$)$_2$ in THF at 0 °C for 0.5 h or to oxazolines **23**, R = *t*-Bu (92%) and **23**, R = C_6H_5 (93%), by exposure to 2 equiv of Et_3N and 0.2 equiv of DBU in DME at reflux for 4 h.



22, R = *t*-Bu or C_6H_5



23, R = *t*-Bu or C_6H_5

Acknowledgment. X.G. is the recipient of an NSERC Postdoctoral Fellowship (Canada).

Supporting Information Available: Experimental procedures for the reactions described herein and characterization data for reaction products. X-ray crystallographic data for bromoamides **17** and **18**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(2) Kürti, L.; Czako, B. *Strategic Applications of Named Reactions in Organic Synthesis*; Elsevier Inc.: Amsterdam, 2005; pp 382−383.

(3) The literature contains sporadic examples of the trapping of bromonium ions by CH_3CN. See: (a) Hassner, A.; Levy, L. A.; Gault, R. *Tetrahedron Lett.* **1966**, 3119−3123. (b) Ye, C.; Schreeve, J. M. *J. Org. Chem.* **2004**, *69*, 8561−8563. (c) Belluci, G.; Bianchini, R.; Chiappe, C. *J. Org. Chem.* **1991**, *56*, 3067−3073.

JA063675W