ORGANIC LETTERS

2011
Vol. 13, No. 9
2448–2451

N-Bromosuccinimide Initiated One-Pot Synthesis of Imidazoline

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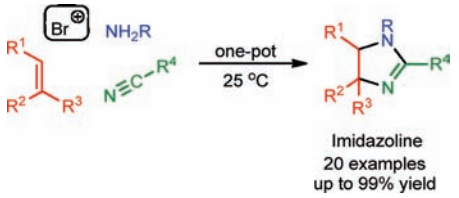
Received March 15, 2011

ABSTRACT



A novel cationic Br initiated one-pot imidazoline synthesis has been developed using olefin, nitrile, amine, and *N*-bromosuccinimide. The olefinic substrates and the nitrile partners can be flexibly varied to achieve a range of imidazoline derivatives.

Nitrogen containing heterocyclic compounds are of great interest in many areas.[1] Important examples include amidines and imidazolines; these compounds are the fundamental units of natural products,[2] biologically active molecules,[3] organocatalysts,[4] and metal complexation ligands.[5] In particular, imidazolines have attracted much attention as they can easily be transformed into imidazoles which are well-known scaffolds that appear in several highly significant biomolecules.[6] Moreover, imidazolines can be hydrolyzed to yield the 1,2-diamine which is often used for the synthesis of organocatalysts and the metal complexation ligands.[7] Many research endeavors have been dedicated to the development of efficient and environmentally benign approaches to the synthesis of these compounds over the past few decades.[3,8] However, apart from long and inefficient synthetic sequences, potentially hazardous azide reagents and/or metallic reagents are commonly used to introduce the nitrogen functionalities in the literature processes which hinder their application in the manufacturing sector.[9]

On the other hand, the Ritter-type reactions, which involve an amine-captured nitronium intermediate, appear to offer an attractive strategy for the construction of imidazoline. To our surprise, sporadic cases have been reported using this approach, the results returned showing limited scope, low yielding reactions, and/or low selectivity. In addition, a catalyst is usually required to

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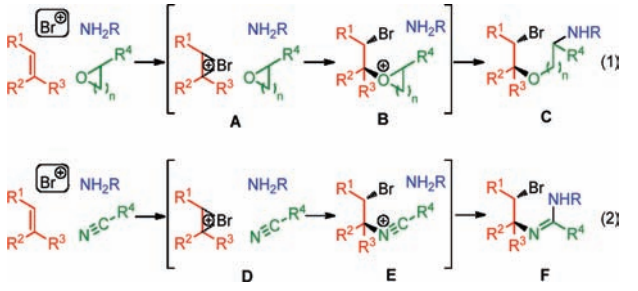
10.1021/ol2006902
Published on Web 04/12/2011

activate the halogen source (e.g., *N*-haloamide) to mediate the electrophilic halogenation.[10]

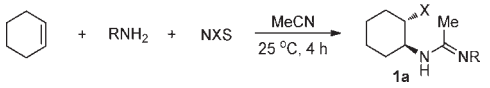
In the course of our effort to develop electrophilic cascades that use the brominating source, *N*-bromosuccinimide (NBS), we reported a novel one-pot electrophilic aminoalkoxylation reaction that used an olefin, NBS, a cyclic ether, and a sulphonamide (Scheme 1, eq 1).[11] The process was highly efficient and involved no additional NBS activator. Several bioactive morpholine derivatives were prepared efficiently using this electrophilic process. The cascade sequence starts with a nucleophilic attack of bromonium ion **A** by a cyclic ether to yield oxonium intermediate **B**. Subsequent attack of **B** by a sulfonamide gives the desired aminoether derivative **C**. We rationalized that instead of a cyclic ether, a nitrile could be used which, in principle, suggested that a halo-amidine derivative could be prepared through a **D**→**E**→**F** sequence (Scheme 1, eq 2).

Scheme 1. Bromonium Ion Promoted Electrophilic Cascades



Thus, an initial experiment was performed using cyclohexene, NBS, acetonitrile, and tosyl amide at 25 °C. As expected, the corresponding bromoamidine **1a** was obtained in 92% yield (Table 1, entry 1).[12] In addition to tosyl amide, other electron-deficient amides including $PhSO_2NH_2$, *p*-$MeOPhSO_2NH_2$, $NsNH_2$, $MsNH_2$, CCl_3CONH_2, and CF_3CONH_2 worked equally well (Table 1, entries 5−10). On the other hand, dialkyl amines or electron-rich amides such as acetamide were unable to offer any desired product. In addition, other halogen sources such as *N*-chlorosuccinimide (NCS) or *N*-iodosuccinimide (NIS) were found to be less reactive (Table 1, entries 11−12). Interestingly, the addition of Lewis acids resulted in a decrease

Table 1. Synthesis of Amidine **1a** Using Various Amides



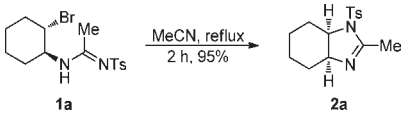
entry[a]	R	NXS	X	yield[e] (%)
1	***Ts***	***NBS***	***Br***	***92***
2[b]	Ts	NBS	Br	90
3[c]	Ts	NBS	Br	60
4[d]	Ts	NBS	Br	61
5	$PhSO_2$	NBS	Br	90
6	$pMeOC_6H_4SO_2$	NBS	Br	81
7	***Ns***	***NBS***	***Br***	***91***
8	Ms	NBS	Br	83
9	CCl_3CO	NBS	Br	87
10	CF_3CO	NBS	Br	90
11	Ts	NCS	Cl	24
12	Ts	NIS	I	26

[a] Reactions were carried out with cyclohexene (0.6 mmol), NXS (0.6 mmol), and RNH_2 (0.5 mmol) in MeCN (3 mL) at 25 °C for 4 h. [b] 1.0 g scale. [c] $SnCl_4$ (0.2 mmol) was used. [d] $Cu(OTf)_2$ (0.1 mmol) was used. [e] Isolated yield.

in reaction yield (Table 1, entries 3−4).[13] It is noteworthy that the reaction is readily scalable without loss of efficiency (Table 1, entry 2). In addition, the performance of the reaction is not affected when the addition sequence is changed. Compound **1a** can be converted to imidazoline **2a** (95% yield) simply by heating in MeCN at reflux for 2 h (Scheme 2).

Having proven the concept of this multicomponent bromoamidine synthesis, we further expanded its scope by varying the olefinic substrates (Table 2). In most cases,

Scheme 2. Synthesis of **2a**



the corresponding imidazolines **2** were obtained as the sole products, a result of intramolecular cyclization of the bromoamidine **1**.[14] Interestingly, a ring-opening product **2f** (87%) was obtained when α-pinene was used, probably through a bromonium ion-initiated rearrangement (Scheme 3). The structures of **1a**, **2f**, and **2m** were confirmed by

(10) Sporadic reports related to this type of cascade: (a) Booker-Milburn, K. I.; Guly, D. J.; Cox, B.; Procopiou, P. A. *Org. Lett.* **2003**, *5*, 3313–3315. (b) Abe, T.; Takeda, H.; Miwa, Y.; Yamada, K.; Yamada, R.; Ishikura, M. *Helv. Chim. Acta* **2010**, *93*, 233–241. (c) Crookes, B.; Seden, T. P.; Turner, R. W. *J. Chem. Soc., Chem. Commun.* **1968**, 342.

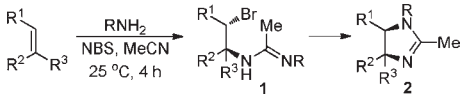
(11) (a) Zhou, L.; Tan, C. K.; Zhou, J.; Yeung, Y.-Y. *J. Am. Chem. Soc.* **2010**, *132*, 10245–10247. For recent examples of electrophilic Br initiated cascades, see:(b) Snyder, S. A.; Treitler, D. S. *Angew. Chem., Int. Ed.* **2009**, *48*, 7899–7903. (c) Snyder, S. A.; Treitler, D. S.; Brucks, A. P. *J. Am. Chem. Soc.* **2010**, *132*, 14303–14314. (d) Alcaide, B.; Almendros, P.; Luna, A.; Torres, M. R. *Adv. Synth. Catal.* **2010**, *352*, 621–626.

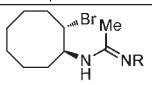
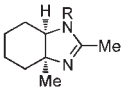
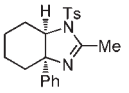
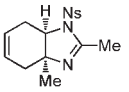
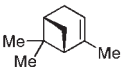
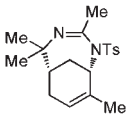
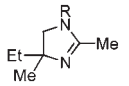
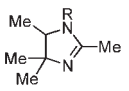
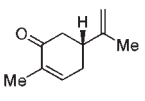
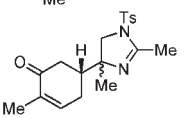
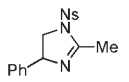
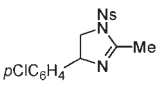
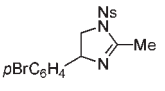
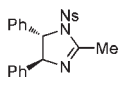
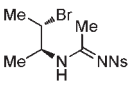
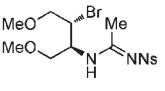
(12) The details appear in the Supporting Information.

(13) An acid catalyst or a highly electrophilic halogen source is usually required to promote the cohalogenation. For a related Ritter-type reaction, see: (a) Hassner, A.; Levy, L. A.; Gault, R. *Tetrahedron Lett.* **1966**, *7*, 3119–3123. (b) Bellucci, G.; Bianchini, R.; Chiappe, C. *J. Org. Chem.* **1991**, *56*, 3067–3073. (c) Yeung, Y.-Y.; Gao, X.; Corey, E. J. *J. Am. Chem. Soc.* **2006**, *128*, 9644–9645.

(14) Representative procedure: To a solution of *N*-bromosuccinimide (107 mg, 0.6 mmol) and sulfonamide (0.5 mmol) in dry acetonitrile (3 mL) in the dark was added olefin (0.6 mmol). After stirring for 4 h at 25 °C, the reaction was quenched with saturated $Na_2S_2O_3$ (5 mL) and $NaHCO_3$ (5 mL). The mixture was extracted with CH_2Cl_2 (3 × 15 mL). The combined extracts were washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography to yield the corresponding product.

Table 2. One-Pot Synthesis of Amidines and Imidazolines Using Various Olefins

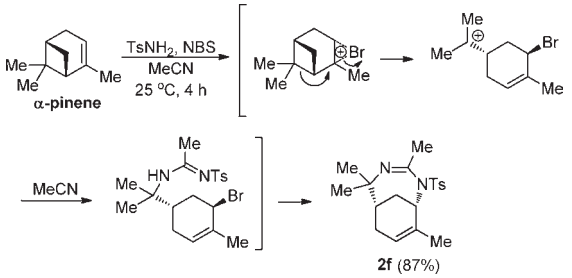


entry[a]	substrate	product		yield[d] (%)
1			**1b**	(R = Ts) 84 (R = Ns) 86
2			**2c**	(R = Ts) 93 (R = Ns) 86
3			**2d**	76
4			**2e**	72
5			**2f**	87
6[b]			**2g**	(R = Ts) 99 (R = Ns) 91
7[b]			**2h**	(R = Ts) 86 (R = Ns) 87
8			**2i**	95
9[c]			**2j**	77
10[c]			**2k**	63
11[c]			**2l**	74
12			**2m**	45
13			**1n**	50
14			**1o**	47

[a] Reactions were carried out with olefin (0.6 mmol), NBS (0.6 mmol), and RNH_2 (0.5 mmol) in MeCN (3 mL) at 25 °C for 4 h. The yields were isolated yields. [b] 1.0 mmol of olefin was used. [c] The reaction time was 16 h. [d] Isolated yield.

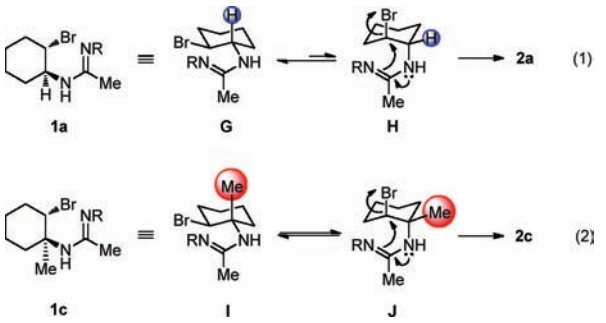
X-ray crystallographic studies.[12] The general features of this reaction include (1) high regioselectivity wherein only

Scheme 3. Proposed Mechanism for the Formation of **2f**



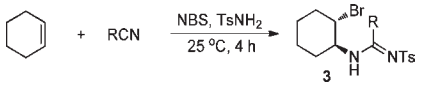
the Markovnikov-type products were isolated (Table 2, entries 2–11); (2) high positional selectivity whereby the more electron-rich olefins react more readily (Table 2, entries 4 and 8); (3) high stereoselectivity which only leads

Scheme 4. Proposed Mechanisms for the Haloamidine Cyclizations of **1a** and **1c**



to the *trans*-bromoamidines from (*E*)-alkenes, and the *cis*-imidazolines when (*Z*)-alkenes are used (Table 2, entries 1–4, 13, and 14)—indeed, a *trans*-imidazoline was isolated

Table 3. Synthesis of Amidines Using Various Nitriles



entry[a]	R	product	yield[b] (%)
1	Et	**3a**	88
2	*n*Pr	**3b**	73
3	*i*Pr	**3c**	81
4	CH=CH$_2$	**3d**	86
5	Ph	**3e**	53

[a] Reactions were carried out with cyclohexene (0.6 mmol), NBS (0.6 mmol), and $TsNH_2$ (0.5 mmol) in RCN (1 mL) at 25 °C for 4 h. [b] Isolated yield.

as the sole product when a *trans*-olefin was used (Table 2, entry 12); and (4) disubstituted olefinic substrates (Table 1,

entry 1; Table 2, entry 1) that provide the haloamidine products while the trisubstituted olefinic substrates afford the imidazoline products under the standard reaction conditions; this can be attributed to a difference in the conformation of the substrates (Scheme 4). Taking **1a** and **1c** as examples, for haloamidine **1a**, the most stable conformer is **G** with the two substituents in equatorial positions (Scheme 4, eq 1). **G** can be isomerized to the less stable conformer **H** in order to cyclize to imidazoline **2a**. Alternatively, in the **1c**→**2c** transformation (Scheme 4, eq 2), the **J/I** ratio appears to be higher than the **H/G** ratio as the steric stress of the methyl group in **I** is released in conformer **J** (equatorial methyl). Nevertheless, the difficulty in cyclization of **1a** (comparing to **1c**) could be overcome by heating up the reaction mixture (cf. Scheme 2).

The scope of this amidine synthesis appears to be quite broad not only with regards to the olefinic component but also in terms of the nitrile partner. A variety of nitriles were found to react with cyclohexene, NBS, and $TsNH_2$ to yield amidines **3a**–**e** in good yields (Table 3).

In summary, we have developed a general and efficient one-pot imidazoline synthesis that uses an olefin, NBS, an amide, and a nitrile. A wide range of imidazoline derivatives can be synthesized using this methodology. This type of reaction is highly practical in several aspects: (1) all the reagents, especially the cascade initiator NBS, are inexpensive and commercially available; (2) the reaction setup is very convenient, involving a simple mixing of the components at room temperature, and a change in the addition sequence does not affect its efficiency; and (3) the reaction is readily scalable. Research toward the exploration of reactions that are analogous to this methodology, as well as the synthesis of bioactive imidazoline derivatives, is underway.

Acknowledgment. We are thankful for the financial support from the National University of Singapore (Grant No. 143-000-428-112).

Supporting Information Available. Experimental procedures and additional information. This material is available free of charge via the Internet at http://pubs.acs.org.