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Additive-Free Nucleophilic Addition of Imidazolines and Imidazoles to Haloacetylenes

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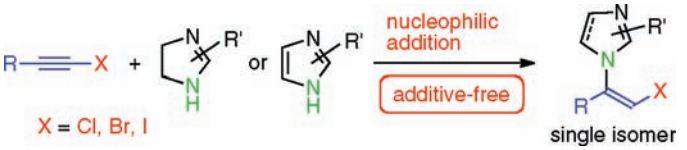
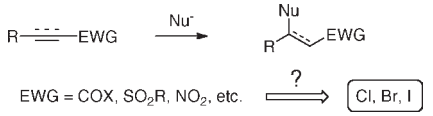
ABSTRACT



Nucleophilic addition of imidazolines to 1-halo-1-alkynes takes place by simple heating in DMF without any additives to give (*Z*)-*N*-(1-halo-1-alken-2-yl)-imidazolines in good yield and in a highly regio- and stereoselective manner. These reaction conditions are also valid for the similar addition of imidazoles.

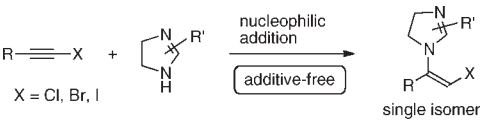
Nucleophilic addition to an electron-deficient carbon–carbon multiple bond is one of the most fundamental reactions in organic chemistry.[1] While various potential electron-withdrawing groups (EWGs) adjacent to olefin or acetylene are utilized for this process, the weakest possible substituents, such as halogens, are also a subject of interest, as shown in Scheme 1.[2−4] Recent studies along this line revealed that certain nucleophiles undergo addition to 1-halo-1-alkynes.[5−7] However, these feasible

Scheme 1. Halogen as an EWG in Nucleophilic Addition



nucleophiles are still limited, and some of them require a promoter such as transition metal catalysts, making the addition mechanism equivocal.[7] To enhance the role of a halide group as shown in Scheme 1, we report here that imidazolines, frequently found as constituents of naturally occurring products or artificial pharmaceuticals,[8] undergo a nucleophilic addition to haloacetylenes, by

Scheme 2. Addition of Imidazolines to Haloacetylenes



† These authors contributed equally to this work.

(1) (a) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry*, 5th ed.; Springer: New York, 2007; Part B, pp 183–200. (b) Smith, M. B.; March, J. *March's Advanced Organic Chemistry*, 6th ed.; Wiley: New Jersey, 2007; pp 1130–1132. (c) *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 4.

(2) For the reactions of fluoro- or polyhalo-substituted olefins and acetylenes, see: (a) Chambers, R. D. *Fluorine in Organic Chemistry*; Wiley: New York, 1973. (b) Tanimoto, S.; Taniyasu, R.; Takahashi, T.; Miyake, T.; Okano, M. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 1931–1936. (c) Kende, A. S.; Fludzinski, P.; Hill, J. H.; Swenson, W.; Clardy, J. *J. Am. Chem. Soc.* **1984**, *106*, 3551–3562. (d) Moyano, A.; Charbonnier, F.; Greene, A. E. *J. Org. Chem.* **1987**, *52*, 2919–2922. (e) Geary, L. M.; Hultin, P. G. *J. Org. Chem.* **2010**, *75*, 6354–6371.

(3) For reviews on nucleophilic addition to haloacetylenes, see: (a) Chambers, R. D.; James, S. R. In *Comprehensive Organic Chemistry*; Barton, D., Ollis, W. D., Stoddart, J. F., Eds.; Pergamon Press: Oxford, 1979; Vol. 1, pp 557–560. (b) Himbert, G. In *Methoden der Organischen Chemie (Houben-Weyl)*; Kropf, H., Schaumann, E., Eds.; Georg Thieme: Stuttgart, 1993; Vol. E15, Part 3, pp 3319–3329.

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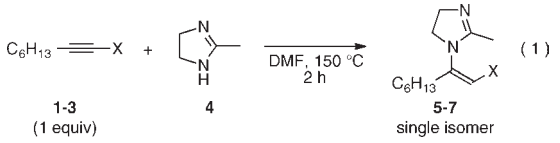
only heating in an appropriate solvent without any additives (Scheme 2).

During our study on the reactions of haloacetylenes,[5d,9] we found that imidazolines undergo facile nucleophilic addition to haloacetylenes. Table 1 summarizes fundamental data regarding the addition of methylimidazoline **4** to various 1-halo-1-octynes (halo = Cl, Br, or I). Among

Table 1. Fundamental Data for Nucleophilic Addition

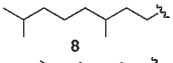
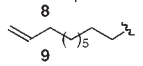
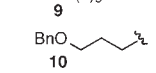
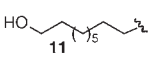
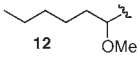
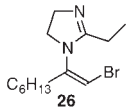
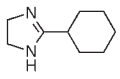
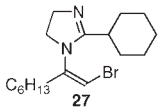
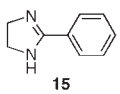
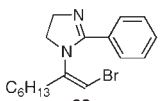
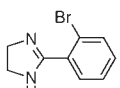
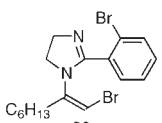
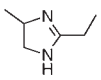
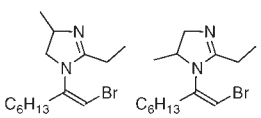
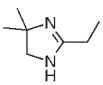
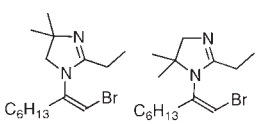
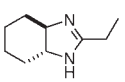
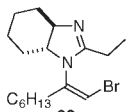
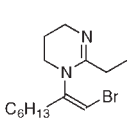


	haloacetylene			product	
entry	X		**4** (equiv)		yield[a] (%)
1	Cl	**1**	2	**5**	75
2	Br	**2**	2	**6**	84
3	I	**3**	2	**7**	41
4	Br	**2**	1.5	**6**	[66]
5	Br	**2**	1	**6**	[36]

[a] Isolated yield based on haloacetylene. Values in brackets were determined by ^{1}H NMR using an internal standard.

the three haloacetylenes **1**–**3** (entries 1–3), bromoacetylene **2** showed the best result, affording (*Z*)-1-bromo-2-(1-imidazolinyl)-1-octene (**6**) in good yield and virtually as a single olefinic isomer (entry 2). For these reactions,

Table 2. Preparation of Various (*Z*)-(1-Bromo-2-alkenyl)imidazolines[a]

entry	bromoacetylene	imidazoline	product	yield (%)[b]
	R—≡—Br			
1	R = C_6H_{13} **2**	 **4**	**6**	84
2	 **8**	**4**	**21**	74
3	 **9**	**4**	**22**	78
4	 **10**	**4**	**23**	75
5	 **11**	**4**	**24**	81
6	 **12**	**4**	**25**	69
7	**2**	 **13**	 **26**	77
8	**2**	 **14**	 **27**	74
9	**2**	 **15**	 **28**	50[c]
10	**2**	 **16**	 **29**	59[c]
11	**2**	 **17**	 **30** 66:34	90[d]
12	**2**	 **18**	 **31** 83:17	83[d]
13	**2**	 **19**[e]	 **32**	69
14	**2**	 **20**	 **33**	75

[a] The reactions were performed with bromoacetylene (1 equiv) and imidazoline (2 equiv) in DMF at 150 °C for 2 h. [b] Isolated yield based on haloacetylene. [c] Imidazoline (1.1 equiv) was used. [d] Combined yield of regioisomers. [e] Racemic sample.

(4) For brief survey of synthetic utility of haloacetylenes, see: (a) Miller, S. I.; Dickstein, J. I. *Acc. Chem. Res.* **1976**, *9*, 358–363. (b) Trofimov, A.; Chernyak, N.; Gevorgyan, V. *J. Am. Chem. Soc.* **2008**, *130*, 13538–13539.

(5) For addition of hydride, see: (a) Zweifel, G.; Lewis, W.; On, H. P. *J. Am. Chem. Soc.* **1979**, *101*, 5101–5102. Halides: (b) Tanaka, R.; Zhéng, S.-Q.; Kawaguchi, K.; Tanaka, T. *J. Chem. Soc., Perkin Trans. 2* **1980**, 1714–1720. (c) Chen, Z.; Jiang, H.; Li, Y.; Qi, C. *Chem. Commun.* **2010**, *46*, 8049–8051. Sulfonamide: (d) Yamagishi, M.; Nishigai, K.; Hata, T.; Urabe, H. *Org. Lett.* **2011**, *13*, 4873–4875. Addition of thiols was mentioned as an intermediate in the reaction of 1,1-dibromoolefins and a few nucleophiles: (e) Xu, H.; Gu, S.; Chen, W.; Li, D.; Dou, J. *J. Org. Chem.* **2011**, *76*, 2448–2458.

(6) For intramolecular nucleophilic addition to haloacetylene, see the followings. With amino group: (a) Elokhina, V. N.; Yaroshenko, T. I.; Nakhmanovich, A. S.; Albanov, A. I. *Russ. J. Org. Chem.* **2006**, *42*, 1866–1867. (b) Elokhina, V. N.; Nakhmanovich, A. S.; Larina, L. I.; Yaroshenko, T. I.; Amosova, S. V. *Russ. J. Org. Chem.* **2009**, *45*, 226–228. With hydroxy group: (c) Grandjean, D.; Pale, P.; Chuche, J. *Tetrahedron Lett.* **1992**, *33*, 4905–4908. (d) Nakhmanovich, A. S.; Elokhina, V. N.; Larina, L. I.; Abramova, E. V.; Lopyrev, V. A. *Russ. J. Gen. Chem.* **2005**, *75*, 437–439. (e) Miao, Z.; Xu, M.; Hoffmann, B.; Bernet, B.; Vasella, A. *Helv. Chim. Acta* **2005**, *88*, 1885–1912.

(7) For transition-metal-catalyzed addition of nucleophiles to haloacetylenes has been reported. Under Cu catalysis, see: (a) Das, B.; Reddy, G. C.; Balasubramanyam, P.; Salvanna, N. *Synthesis* **2011**, 816–820. (b) Burley, G. A.; Davies, D. L.; Griffith, G. A.; Lee, M.; Singh, K. *J. Org. Chem.* **2010**, *75*, 980–983. For a reaction that is proposed to involve Ag-catalyzed addition, see: (c) Chen, Z.; Li, J.; Jiang, H.; Zhu, S.; Li, Y.; Qi, C. *Org. Lett.* **2010**, *12*, 3262–3265. For intramolecular additions under Au catalysis, see: (d) Buzas, A. K.; Istrate, F. M.; Gagosz, F. *Tetrahedron* **2009**, *65*, 1889–1901. (e) Harkat, H.; Dembelé, A. Y.; Weibel, J.-M.; Blanc, A.; Pale, P. *Tetrahedron* **2009**, *65*, 1871–1879. (f) Buzas, A.; Gagosz, F. *Org. Lett.* **2006**, *8*, 515–518. For reviews on relevant metal-mediated hydroamination of acetylenes, see: (g) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079–3159. (h) Pohlki, F.; Doye, S. *Chem. Soc. Rev.* **2003**, *32*, 104–114.

no particular additives are necessary, and simple heating in DMF proved good enough as shown in eq 1.[10] If desired, chloro-derivative **5** can be prepared albeit in a somewhat lower yield and iodo-derivative **7** in a moderate yield (entries 1 and 3). In each case, other regio- and stereoisomers were not detected in the crude reaction mixture. The use of excess imidazoline (2 equiv to haloacetylene) is preferable to afford good yields (entries 2 vs 4 and 5). As this reaction does not need any additives, including transition metal salts, it is most likely categorized as nucleophilic addition of imidazolines to an electron-deficient acetylenic bond.[11]

Other products obtained by this method are summarized in Table 2. Entries 2−6 show that the mild reaction conditions allow the presence of various functional groups, involving an unprotected hydroxy group, on the side chain of bromoacetylenes **8**−**12**. For a substituent at the 2-position of imidazoline, the more sterically hindered ethyl and cyclohexyl groups in **13** and **14** are acceptable to give **26** and **27**, respectively (entries 7 and 8). When 2-arylimidazolines **15** and **16** were used in slight excess (1.1 equiv to **2**) (entries 9 and 10), addition products **28** and **29** were obtained in yields better than that of 2-alkylimidazoline **4** (cf. entry 5, Table 1). Unsymmetrically substituted imidazoline **17** or **18** afforded a mixture of 1,2,4- and 1,2,5-trisubstituted imidazolines **30** or **31**, respectively (entries 11 and 12), but their combined yields remain good to excellent. Likewise, 2,4,5-trisubstituted symmetrical imidazoline **19** afforded **32** in good yield (entry 13). Besides the above imidazolines, 1,4,5,6-tetrahydropyrimidine **20**, a six-membered analogue of imidazoline, also afforded the desired product **33** in good yield (entry 14). The exceptional simplicity of this reaction prompted us to examine its extension to *imidazoles*, an aromatic analogue of *imidazoline*. Although a couple of recent reports already deal with the addition of *imidazoles* to bromoacetylenes in the presence of copper catalysts,[12] we disclose here our own findings that their addition, in fact, proceeds under the additive-free conditions. Table 3 summarizes these results obtained according to eq 1, except the prolonged reaction period (24 h rather than 2 h). As extra additives to promote the addition are not necessary at all, the reaction conditions appear to be mild enough to allow the presence of typical functional groups such as olefin, hydroxy group, and ketone on the side chain of bromoacetylenes **34**−**36**, affording desired products **44**−**46** in good yields (entries 2−4). Other types of imidazoles **38**−**42** also afforded the expected products **47**−**51** in good yields (entries 5−9).

In conclusion, (*Z*)-*N*-(1-halo-1-alken-2-yl)imidazolines and (*Z*)-*N*-(1-bromo-1-alken-2-yl)imidazoles, versatile intermediates in organic synthesis yet otherwise tedious to prepare, are conveniently synthesized by the nucleophilic

Table 3. Preparation of Various (*Z*)-(1-Bromo-2-alkenyl)imidazoles

entry	bromoacetylene	imidazole	product	yield (%)[a]
1	R = C_6H_{13} **2**	**37**	**43**	72
2	**34**	**37**	**44**	78
3	**35**	**37**	**45**	73
4	**36**	**37**	**46**	56
5	**2**	**38**	**47**	81
6	**2**	**39**	**48**	88
7	**2**	**40**	**49** 57:43 (or *vice versa*)	58
8	**2**	**41**	**50**	71
9	**2**	**42**	**51**	80

[a] Isolated yields.

(8) For recent examples, see: (a) Guinchard, X.; Vallée, Y.; Denis, J.-N. *Org. Lett.* **2007**, *9*, 3761–3764. (b) Kahlon, D. K.; Lansdell, T. A.; Fisk, J. S.; Hupp, C. D.; Friebe, T. L.; Hovde, S.; Jones, A. D.; Dyer, R. D.; Henry, R. W.; Tepe, J. J. *J. Med. Chem.* **2009**, *52*, 1302–1309. (c) Giorgioni, G.; Ambrosini, D.; Vesprini, C.; Hudson, A.; Nasuti, C.; Di Stefano, A.; Sozio, P.; Ciampi, O.; Costa, B.; Martini, C.; Carrieri, A.; Carbonara, G.; Enzensperger, C.; Pigini, M. *Bioorg. Med. Chem.* **2010**, *18*, 7085–7091.

(9) (a) Fukudome, Y.; Naito, H.; Hata, T.; Urabe, H. *J. Am. Chem. Soc.* **2008**, *130*, 1820–1821. (b) Hirano, S.; Fukudome, Y.; Tanaka, R.; Sato, F.; Urabe, H. *Tetrahedron* **2006**, *62*, 3896–3916. (c) Hirano, S.; Tanaka, R.; Urabe, H.; Sato, F. *Org. Lett.* **2004**, *6*, 727–729.

(10) These reaction conditions have been optimized. Various bases as additive did not show any beneficial influence.

(11) An alternative radical mechanism seems unlikely, as radical inhibitors such as BHT or galvinoxyl did not suppress the progress of the reaction.

(12) See refs 7a and 7b. The addition of imidazoles to 1,1-dibromoolefins was also performed in the presence of TBAF (Bu_4NF) as an additive (ref 5e). Compatibility with the functional groups shown in entries 2−4 of Table 3 has not been addressed in these copper- or TBAF-mediated reactions.

addition of imidazolines or imidazoles to haloacetylenes. These reactions proceed under additive-free conditions, with simple experimental operation, and in good yield and with exclusive regio- and stereoselectivities. The compatibility with representative functional groups should be advantageous for practical application of this method, which is underway in our laboratory.

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