ORGANIC LETTERS

2011
Vol. 13, No. 18
4873–4875

Nucleophilic Addition of Sulfonamides to Bromoacetylenes: Facile Preparation of Pyrroles

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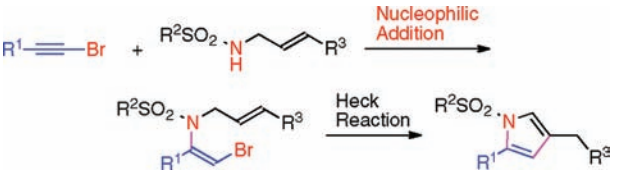
Received July 20, 2011

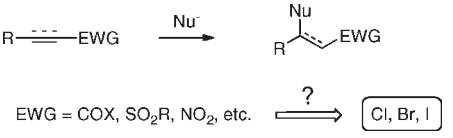
ABSTRACT



Nucleophilic addition of sulfonamides to 1-bromo-1-alkynes provided (*Z*)-*N*-(1-bromo-1-alken-2-yl)-*p*-toluenesulfonamides in good yield and in a highly regio- and stereoselective manner. Treatment of product (*Z*)-*N*-(1-bromo-1-octen-2-yl)-*N*-allyl-*p*-toluenesulfonamide with a palladium catalyst under Heck conditions afforded 1-(*p*-toluenesulfonyl)-2-hexyl-4-methylpyrrole in good yield. Other pyrroles with various substituents can also be prepared in good yield by this method.

Nucleophilic addition to an electron-deficient carbon–carbon multiple bond is one of the most fundamental reactions in organic chemistry.[1] Various potential electron-withdrawing groups (EWGs) adjacent to olefin or acetylene are utilized for this process, as shown in Scheme 1. On the other hand, the weakest possible substituents, such as halogens, that serve as EWG should also be a subject of interest. However, haloolefins and haloacetylenes, except fluoro- or polyhalo-substituted compounds,[2] have not been widely investigated in this regard.[3] In this study, we show that haloacetylenes undergo nucleophilic addition by sulfonamides to give functionalized olefins, which can be readily applied to a concise preparation of pyrroles, as shown in Scheme 2.

Scheme 1. Halogen as an EWG in Nucleophilic Addition



During our study on reactions of sulfonamides,[4] we encountered their facile addition to haloacetylenes.[5−7] Table 1 summarizes some fundamental data relating to the use of various halogenated (Cl, Br, and I) 1-octynes and standard reaction conditions regarding additive, solvent, temperature, and reaction period are given in eq 1. Among the three haloacetylenes **1**−**3** (entries 1−3), bromoacetylene **2** showed the best results, affording (*Z*)-1-bromo-2-(sulfonylamino)-1-octene (**6**) in good yield and in a highly regio- and stereoselective manner. Other isomeric products were not detected

(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 York, 2007; pp 1130−1132. (c) Trost, B. M.; Fleming, I., Eds. *Comprehensive Organic Synthesis*; Pergamon Press: Oxford, 1991; Vol. 4.

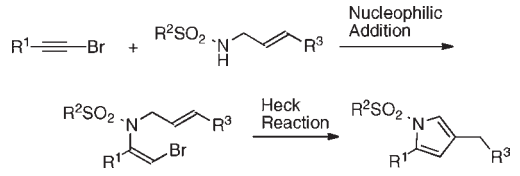
(2) (a) Chambers, R. D. *Fluorine in Organic Chemistry*; Wiley: New York, 1973. (b) Tanimoto, S.; Taniyasu, R.; Takahashi, T.; Miyake, T.; Okano, M. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 1931–1936. (c) Kende, A. S.; Fludzinski, P.; Hill, J. H.; Swenson, W.; Clardy, J. *J. Am. Chem. Soc.* **1984**, *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 brief survey of synthetic utility of haloacetylenes, see: (a) Trofimov, A.; Chernyak, N.; Gevorgyan, V. *J. Am. Chem. Soc.* **2008**, *130*, 13538–13539. (b) Miller, S. I.; Dickstein, J. I. *Acc. Chem. Res.* **1976**, *9*, 358–363.

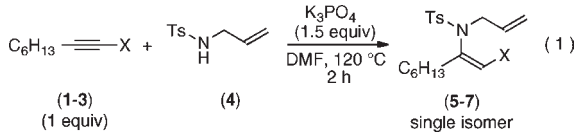
(4) (a) Fukudome, Y.; Naito, H.; Hata, T.; Urabe, H. *J. Am. Chem. Soc.* **2008**, *130*, 1820–1821. (b) Naito, H.; Hata, T.; Urabe, H. *Org. Lett.* **2010**, *12*, 1228–1230. (c) Kato, Y.; Yen, D. H.; Fukudome, Y.; Hata, T.; Urabe, H. *Org. Lett.* **2010**, *12*, 4137–4139.

10.1021/ol201952b
Published on Web 08/15/2011

Scheme 2. Two-step Preparation of Pyrroles



in the crude reaction mixture. The use of excess sulfonamide (2−3 equiv to bromoacetylene) is preferable to afford good yields (entries 2 and 4 vs 5). However, in a typical run (entry 2), the unreacted sulfonamide was completely recovered and may be recycled; therefore, the yield of product **6** was calculated to be quantitative based on consumed sulfonamide **4**. Although a precise mechanism of this reaction is not presently clear, it can be formally categorized as nucleophilic addition of sulfonamides to an electron-deficient acetylenic bond.



While the aforementioned reaction is operationally quite simple, the products, 1-bromo-2-(sulfonylamino)-1-alkenes with defined stereochemistry, are otherwise tedious to prepare but are versatile synthetic intermediates. For instance, the *cis* alignment of vinyl bromide and the incoming

Table 1. Fundamental Data for Nucleophilic Addition

	haloacetylene			product	
entry	X		**4** (equiv)	yield (%)[a]	recovered **4** (%)[b]
1	Cl	**1**	3	**5** 54, 65[c]	
2	Br	**2**	3	**6** 74, quant.[d]	76
3	I	**3**	3	**7** (7), (6)[e]	
4	Br	**2**	2	**6** 71	
5	Br	**2**	1.5	**6** (54)[f]	

[a] Isolated yield based on haloacetylene. Values in parentheses were determined by ^{1}H NMR using an internal standard. [b] Isolated yield based on **4**. [c] Reaction was continued until **1** was completely consumed (6 h). [d] Yield based on consumed **4**. [e] Reaction was continued until **3** was completely consumed (6 h). [f] Reaction period was extended to 4 h.

nucleophile could be particularly useful for many types of cyclizations. Considering this fact, we investigated the application of these products in a concise preparation of pyrroles according to Scheme 2.[8,9] In fact, upon treating product **6** (Table 1) with a palladium catalyst under Heck conditions,[10] the desired cyclization took place providing pyrrole **8** directly in good yield, as shown in eq 2.[11,12] While various vinyl bromides participate in the Heck reaction,

(5) 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 3320−3321. For addition of hydride or halide, see: (c) Zweifel, G.; Lewis, W.; On, H. P. *J. Am. Chem. Soc.* **1979**, *101*, 5101–5102. (d) Tanaka, R.; Zhéng, S.-Q.; Kawaguchi, K.; Tanaka, T. *J. Chem. Soc., Perkin 2* **1980**, 1714–1720. After almost completing this work, similar nucleophilic addition to haloacetylenes was mentioned as an intermediate in the reaction of 1,1-dibromoolefins and 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 haloacetylenes 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) Transition metal-catalyzed addition of nucleophiles to haloacetylenes has recently appeared. For an intermolecular reaction, 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 intramolecular reactions, see:(c) Buzas, A. K.; Istrate, F. M.; Gagosz, F. *Tetrahedron* **2009**, *65*, 1889–1901. (d) Harkat, H.; Dembelé, A. Y.; Weibel, J.-M.; Blanc, A.; Pale, P. *Tetrahedron* **2009**, *65*, 1871–1879. (e) Buzas, A.; Gagosz, F. *Org. Lett.* **2006**, *8*, 515–518. For reviews on relevant metal-mediated hydroamination of acetylenes, see:(f) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079–3159. (g) Pohlki, F.; Doye, S. *Chem. Soc. Rev.* **2003**, *32*, 104–114.

(8) For reviews on pyrrole synthesis, see: (a) Katritzky, A. R., Rees, C. W., Bird, C. W., Cheeseman, G. W. H., Eds. *Comprehensive Heterocyclic Chemistry*; Pergamon Press: Oxford, 1984; Vol. 4. (b) Gilchrist, T. L. *J. Chem. Soc., Perkin 1* **2001**, 2491–2515. (c) Balme, G. *Angew. Chem., Int. Ed.* **2004**, *43*, 6238–6241. (d) Patil, N. T.; Yamamoto, Y. *Arkivoc* **2007**, 121–141. (e) Bellina, F.; Rossi, R. *Tetrahedron* **2006**, *62*, 7213–7256. (f) Schmuck, C.; Rupprecht, D. *Synthesis* **2007**, 3095–3110.

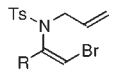
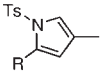
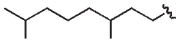
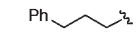
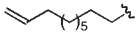
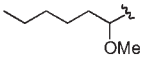
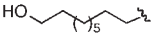
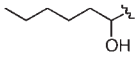
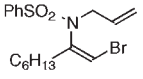
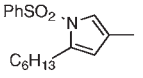
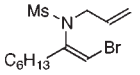
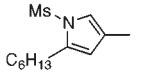
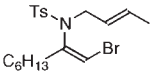
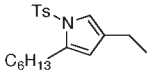
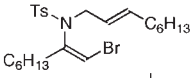
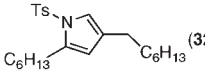
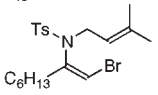
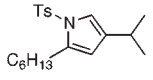
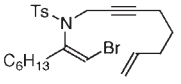
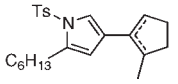
(9) For recent reports on pyrrole synthesis from olefins or acetylenes, see: (a) Trost, B. M.; Lumb, J.-P.; Azzarelli, J. M. *J. Am. Chem. Soc.* **2011**, *133*, 740–743. (b) Stuart, D. R.; Alsabeh, P.; Kuhn, M.; Fagnou, K. *J. Am. Chem. Soc.* **2010**, *132*, 18326–18339. (c) Rakshit, S.; Patureau, F. W.; Glorius, F. *J. Am. Chem. Soc.* **2010**, *132*, 9585–9587. (d) Ribeiro Laia, F. M.; Cardoso, A. L.; Beja, A. M.; Silva, M. R.; Pinho e Melo, T. M. V. D. *Tetrahedron* **2010**, *66*, 8815–8822. (e) Liu, W.; Jiang, H.; Huang, L. *Org. Lett.* **2010**, *12*, 312–315. (f) Peng, H. M.; Zhao, J.; Li, X. *Adv. Synth. Catal.* **2009**, *351*, 1371–1377. (g) Wang, J.-Y.; Wang, X.-P.; Yu, Z.-S.; Yu, W. *Adv. Synth. Catal.* **2009**, *351*, 2063–2066. (h) Mizuno, A.; Kusama, H.; Iwasawa, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 8318–8320. (i) Wyrębek, P.; Sniady, A.; Bewick, N.; Li, Y.; Mikus, A.; Wheeler, K. A.; Dembinski, R. *Tetrahedron* **2009**, *65*, 1268–1275. (j) Aponick, A.; Li, C.-Y.; Malinge, J.; Marques, E. F. *Org. Lett.* **2009**, *11*, 4624–4627. (k) Egi, M.; Azechi, K.; Akai, S. *Org. Lett.* **2009**, *11*, 5002–5005. (l) Merkul, E.; Boersch, C.; Frank, W.; Müller, T. J. J. *Org. Lett.* **2009**, *11*, 2269–2272.

(10) For recent reviews on Heck reaction, see: (a) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009–3066. (b) Whitcombe, N. J.; Hii, K. K. (M.); Gibson, S. E. *Tetrahedron* **2001**, *57*, 7449–7476. (c) Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945–2963. (d) Phan, N. T. S.; Van Der Sluys, M.; Jones, C. W. *Adv. Synth. Catal.* **2006**, *348*, 609–679. (e) Polshettiwar, V.; Molnár, Á. *Tetrahedron* **2007**, *63*, 6949–6976. (f) Felpin, F.-X.; Nassar-Hardy, L.; Le Callonnec, F.; Fouquet, E. *Tetrahedron* **2011**, *67*, 2815–2831.

(11) For relevant cyclization of *N*-allyl-*o*-bromoanilines to indoles, see: (a) Jensen, T.; Pedersen, H.; Bang-Andersen, B.; Madsen, R.; Jørgensen, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 888–890. (b) Majumdar, K. C.; Chakravorty, S.; Shyam, P. K.; Taher, A. *Synthesis* **2009**, 403–408. For a review of intramolecular Heck reaction, see:(c) Link, J. T. In *Organic Reactions*; Overman, L. E., Ed.; Wiley: New York, 2002; Vol. 60, pp 157−534.

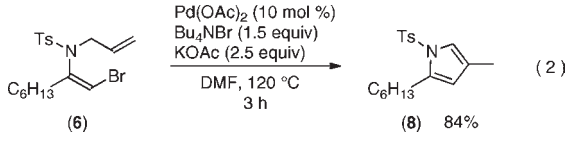
(12) The conditions of eq 2 were adopted from ref 11b and the following: Jeffery, T. *Tetrahedron* **1996**, *52*, 10113–10130. However, in this reaction, 3 mol % of the Pd catalyst was sufficient (84% yield of **8**), but 10 mol % of the catalyst was routinely used to insure the complete reaction in the runs of Table 2. Likewise, when 3 mol % of Pd was used in eq 3, the overall yield of **8** from **2** was 55%.

Table 2. Two-step Synthesis of Pyrroles According to eqs 1 and 2

entry	products of eq 1[a]	yield (%)[b]	products of eq 2[c]	yield (%)[d]
1	 R = C_6H_{13}	(**6**) 74, 71[e]		(**8**) 84
2		(**9**) 76		(**22**) 81
3		(**10**) 71		(**23**) 79
4		(**11**) 76		(**24**) 76
5		(**12**) 73		(**25**) 81
6		(**13**) 67		(**26**) 85
7		(**14**) 72		(**27**) 67
8		(**15**) 65		(**28**) 80
9		(**16**) 71		(**29**) 85
10		(**17**) 74		(**30**) 85
11		(**18**) 73		(**31**) 75[f]
12		(**19**) 66		(**32**) 71[f]
13		(**20**) 74		(**33**) 65[g]
14		(**21**) 78		(**34**) 68[f,h]

[a] Bromoacetylene (1 equiv), sulfonamide (3 equiv), K_3PO_4 (1.5 equiv); DMF, 120 °C, 2 h. [b] Isolated yields based on bromoacetylene. [c] $Pd(OAc)_2$ (10 mol %), Bu_4NBr (1.5 equiv), KOAc (2.5 equiv); DMF, 120 °C, 3 h. [d] Isolated yields. [e] Sulfonamide (2 equiv) was used. [f] Reaction period was 4 h. [g] Reaction period was 8 h; K_3PO_4 was used in place of KOAc. [h] Combined yield of an 87:13 mixture of tetra- and trisubstituted olefinic isomers.

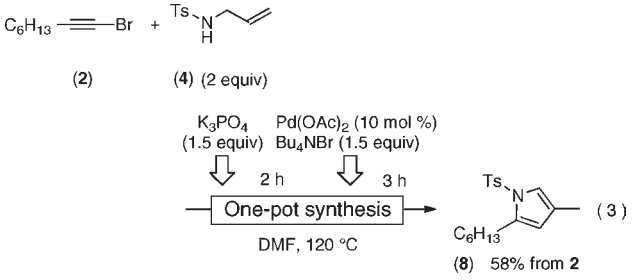
this transformation illustrates its successful application to β-bromoenamine derivatives.[13]



(2)

Table 2 summarizes other results of eqs 1 and 2. Various bromoacetylenes underwent nucleophilic addition of *N*-allyl-*p*-toluenesulfonamides **4** to give corresponding *Z*-bromoolefins **9**–**15** (entries 2–8). The mild reaction conditions allow the presence of various functional groups, including unprotected hydroxy groups (entries 3–8). In addition to *p*-toluenesulfonamides, benzene- and methanesulfonamides showed the same results affording **16** and **17** (entries 9 and 10). Sulfonamides having a higher 2-alkenyl group than allyl (entries 11–13) or a 2-alkynyl group (entry 14) also participated in the addition to give bromoolefins **18**–**21**. Considering the successful preparation of various *Z*-bromoolefins, we proceeded to the next Heck reaction of these intermediates. We found that the desired pyrroles were obtained uniformly in good yields as previously seen for **8** (eq 2). Furthermore, the conditions were compatible with various functionalities including a terminal olefin and hydroxy groups (pyrroles **22**–**28**, entries 2–8). Likewise, both aromatic and aliphatic sulfonamides **16** and **17** afforded pyrroles **29** and **30**, respectively (entries 9 and 10). We emphasize that by appropriately choosing *N*-alkenyl group on the sulfonamide, various 2,4-disubstituted pyrroles, such as **31**–**34**, could be obtained by this method (entries 11–14).

To determine the individual results for each step of the sequence including nucleophilic addition and subsequent Heck cyclization, we listed the results of each process in Table 2. However, pyrroles could be more conveniently prepared by one-pot synthesis, as shown in eq 3, in which the overall yield of **8** (58%)[12] is comparable to that of the corresponding two-step sequence shown in entry 1 of Table 2 (71 × 84 = 60%).



(3)

In conclusion, we report the facile nucleophilic addition of sulfonamides to bromoacetylenes to exclusively give (*Z*)-1-bromo-2-(sulfonylamino)-1-alkenes. These bromoolefins are useful synthetic intermediates that were demonstrated by their application in a concise preparation of pyrroles facilitated by Heck cyclization.

Acknowledgment. This work was supported by a Grant-in-Aid for Challenging Exploratory Research (22655014) from JSPS, Japan.

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.

(13) To the best of our knowledge, aliphatic bromides of this type have not been employed in the Heck reaction.