ORGANIC LETTERS

2004
Vol. 6, No. 10
1581−1584

Efficient Syntheses of Heterocycles and Carbocycles by Electrophilic Cyclization of Acetylenic Aldehydes and Ketones

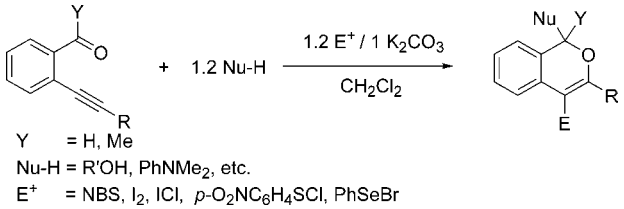
Dawei Yue, Nicola Della Cà, and Richard C. Larock*

Department of Chemistry, Iowa State University, Ames, Iowa 50011

larock@iastate.edu

Received February 21, 2004

ABSTRACT



Highly substituted oxygen heterocycles can be prepared in good yields at room temperature by reacting *o*-(1-alkynyl)-substituted arene carbonyl compounds with NBS, I_2, ICl, *p*-$O_2NC_6H_4SCl$, or PhSeBr and various alcohols or carbon-based nucleophiles. Naphthyl ketones and iodides are readily prepared by the reaction of 2-(1-alkynyl)arene-carboxaldehydes with I_2 and simple olefins or alkynes.

The electrophilic cyclization of functionally substituted alkenes has provided an extremely useful route for the synthesis of a wide variety of heterocyclic and carbocyclic compounds, which have often proven to be useful as intermediates in the synthesis of natural products and pharmaceuticals.[1] The analogous chemistry of alkynes has been far less studied, although it would appear to be a very promising route to an extraordinary range of useful, functionally substituted heterocycles and carbocycles.[2] Our recent work has indicated that benzothiophenes,[3] isoquinolines,[4] and isocoumarins[5] can be easily synthesized by the electrophilic cyclization of appropriate functionally substituted alkynes using iodine-, sulfur-, and selenium-containing electrophiles under exceptionally mild reaction conditions. Others have recently reported a number of very useful analogous iodine-promoted cyclizations of functionally substituted alkynes.[6]

Recently, Yamamoto reported an interesting cyclization of acetylenic aldehydes to 1-alkoxy-1*H*-isochromenes catalyzed by palladium.[7] The Pd(II) salt employed was claimed to exhibit a dual role as both a Lewis acid and a transition-metal catalyst. In a more recent study, the analogous preparation of 1*H*-isochromenes has been achieved upon reaction of bis(pyridine) iodonium tetrafluoroborate (IPy_2BF_4) and HBF_4 with the same acetylenic carbonyl precursors in the presence of various nucleophiles.[8] The use of expensive

(1) (a) Lotagawa, O.; Inoue, T.; Taguchi, T. *Rev. Heteroatom Chem.* **1996**, *15*, 243. (b) Frederickson, M.; Grigg, R. *Org. Prep. Proc. Int.* **1997**, *29*, 33. (c) Cardillo, G.; Orena, M. *Tetrahedron* **1990**, *46*, 3321.

(2) (a) Drenth, W. In *Chemistry of Triple-Bonded Functional Groups*; Patai, S., Ed.; J. Wiley: Chichester, UK, 1994; Vol. 2, pp 873−915. (b) Schmid, G. H. In *The Chemistry of the Carbon−Carbon Triple Bond*; Patai, S., Ed.; J. Wiley: Chichester, UK, 1978; Vol. 1, pp 275−341.

(3) Yue, D.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 1905.

(4) Huang, Q.; Hunter, J. A.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 3437.

(5) Yao, T.; Larock, R. C. *Tetrahedron Lett.* **2002**, *43*, 7401.

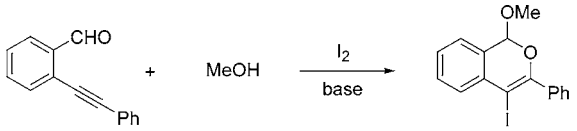
(6) (a) Barluenga, J.; Trincado, M.; Rubio, E.; Gonza'lez, J. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 2406. (b) Knight, D. W.; Redfern, A. L.; Gilmore, J. *J. Chem. Soc., Perkin Trans. 1* **2002**, 622. (c) Arcadi, A.; Cacchi, S.; Giuseppe, S. D.; Fabrizi, G.; Marinelli, F. *Org. Lett.* **2002**, *4*, 2409. (d) Bellina, F.; Biagetti, M.; Carpita, A.; Rossi, R. *Tetrahedron Lett.* **2001**, *42*, 2859. (e) Bellina, F.; Biagetti, M.; Carpita, A.; Rossi, R. *Tetrahedron* **2001**, *57*, 2857. (f) Flynn, B. L.; Verdier-Pinard, P.; Hamel, E. *Org. Lett.* **2001**, *5*, 651. (g) Djuardi, E.; McNelis, E. *Tetrahedron Lett.* **1999**, *40*, 7193. (h) Marshall, J. A.; Yanik, M. M. *J. Org. Chem.* **1999**, *64*, 3798. (i) Arcadi, A.; Cacchi, S.; Fabrizi, G.; Marinelli, F.; Moro, L. *Synlett* **1999**, 1432. (j) Knight, D. W.; Redfern, A. L.; Gilmore, J. *J. Chem. Soc., Chem. Commun.* **1998**, 2207. (k) Redfern, A. L.; Gilmore, J. *Synlett* **1998**, 731. (l) Ren, X.-F.; Konaklieva, M. I.; Shi, H.; Dicy, H.; Lim, D. V.; Gonzales, J.; Turos, E. *J. Org. Chem.* **1998**, *63*, 8898. (m) Bew, S. P.; Knight, D. W. *J. Chem. Soc., Chem. Commun.* **1996**, 1007. (n) El-Taeb, G. M. M.; Evans, A. B.; Jones, S.; Knight, D. W. *Tetrahedron Lett.* **2001**, *42*, 5945.

(7) (a) Asao, N.; Nogami, T.; Takahashi, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **2002**, *124*, 764. (b) Nakamura, H.; Ohtaka, M.; Yamamoto, Y. *Tetrahedron Lett.* **2002**, *43*, 7631.

(8) Barluenga, J.; Vazquez-Villa, H.; Ballesteros, A.; Gonzalez, J. M. *J. Am. Chem. Soc.* **2003**, *125*, 9028.

10.1021/ol049690s CCC: $27.50
Published on Web 04/13/2004

Scheme 1



1 **2**

solvent	MeOH (equiv)	I_2 (equiv)	base (equiv)	yield (%)
CH_2Cl_2	1.2	1.2	K_2CO_3 (1.0)	88
CH_3CN	1.2	1.2	K_2CO_3 (1.0)	40
DMF	1.2	1.2	K_2CO_3 (1.0)	trace
CH_2Cl_2	1.2	1.2	$KHCO_3$ (1.0)	70
CH_2Cl_2	2.0	2.5	K_2CO_3 (1.0)	80
CH_2Cl_2	2.0	2.5	K_2CO_3 (2.0)	78
MeOH	-	2.5	K_2CO_3 (2.0)	68

IPy_2BF_4, together with $B(OMe)_3$ or HBF_4, and the relatively complicated stepwise procedure employed make this approach a bit unwieldy synthetically. Furthermore, the scope of this cyclization has yet to be reported.

We simultaneously found that this three-component reaction[9] proceeds smoothly by using various electrophiles such as I_2, ICl, NBS, *p*-$O_2NC_6H_4SCl$, and PhSeBr to generate the corresponding iodine-, bromine-, sulfur-, and selenium-substituted heterocycles in high yields under very mild reaction conditions. Herein, we wish to report a more convenient and efficient approach to these types of heterocycles involving electrophilic cyclization using a range of electrophiles and nucleophiles.

Our initial studies were aimed at finding optimal reaction conditions for the electrophilic cyclization of the *o*-(1-alkynyl)benzaldehydes. Our investigation began with the reaction of *o*-(phenylethynyl)benzaldehyde (**1**), methanol, and I_2 (Scheme 1). The reaction was first attempted using 0.25 mmol of *o*-(phenylethynyl)-benzaldehyde (**1**), 1.2 equiv of methanol, 1 equiv of K_2CO_3, and 1.2 equiv of I_2 in CH_2Cl_2 at room temperature.

Iodocyclization proceeded smoothly and provided an 88% yield of the desired isochromene product **2**. Other solvents such as CH_3CN and DMF were also investigated and proved to be far less effective. $KHCO_3$ and NEt_3 were also investigated as bases. While $KHCO_3$ provided a slightly lower yield of the desired product than K_2CO_3, NEt_3 proved to be ineffective and none of the desired product was detected. Although CH_2Cl_2 is not a good solvent for K_2CO_3, the presence of K_2CO_3 was crucial for a clean, high-yielding reaction. K_2CO_3 is presumed to neutralize the byproduct HI of the electrophilic cyclization, which can also react with the acetylenic aldehyde and generate the corresponding pyrilium salt.[10] The use of methanol as the reaction solvent resulted in a lower yield. Use of 1.2 equiv of I_2 has proven to be sufficient to achieve a high yield. Further increasing the amount of I_2 did not give better yields.

Based on the above optimization efforts, the combination of 1.2 equiv of nucleophile, 1 equiv of K_2CO_3, 1.2 equiv of I_2, and the use of CH_2Cl_2 as the solvent at room temperature gave the best results. This procedure has been used as our standard reaction conditions for subsequent electrophilic cyclizations. To test the generality of this chemistry, acetylenic aldehydes bearing different substituents on the carbon−carbon triple bond were synthesized in high yields by the palladium/copper-catalyzed coupling of *o*-bromobenzaldehyde and the corresponding terminal alkynes.[11] The resulting acetylenic aldehydes were then allowed to react under our standard electrophilic cyclization conditions to afford the corresponding 1*H*-isochromene products in good to excellent yields. The results are summarized in Table 1.

Alkynes bearing an aromatic ring, as well as alkyl and vinylic substituents, all react well with methanol, *n*-butanol, and 2-iodobenzyl alcohol to provide the desired iodocyclization products in very good yields (entries 1−3, 8, and 11). Interestingly, not only alcohols but also an electron-rich aromatic compound like *N*,*N*-dimethylaniline can be used as a nucleophile, affording iodocyclization products in generally good to excellent yields (entries 4, 9, and 12). Pyridine derivative **16** readily reacted under our standard conditions using I_2 or ICl and provided the desired iodocyclization product in a 64% yield (entries 13 and 14). In all cases, reactions with readily available, inexpensive iodine gave higher yields of isochromene product than the Barluenga process, which used the expensive iodonium salt and HBF_4 (compare Barluenga's results in parentheses with ours).

To further explore the scope of this cyclization, NBS was also used and provided a decent yield of the desired cyclization product (entry 5). Commercially available sulfur and selenium electrophiles have also been employed in this process and have been found to provide very good yields of the desired cyclization products using methanol as the nucleophile (entries 6, 7, and 10). The reactions with *p*-$O_2NC_6H_4SCl$ were complete in a shorter period of time and gave higher yields of products than those with PhSeBr.

α-Acetylenic aryl ketones are also viable substrates for cyclization (see entry 15). It should be noted, however, that ketone **18** reacted smoothly with I_2 to provide a 90% yield of the 5-*exo*-*dig* cyclization product **19**, rather than the six-membered ring ether formed by the electrophilic cyclization of benzaldehyde derivatives. The use of K_2CO_3 again provides very mild basic conditions and avoids the acid-initiated, partial decomposition of this cyclization product described in Barluenga's publication.[8]

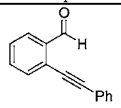
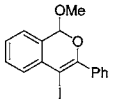
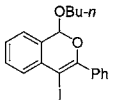
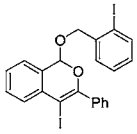
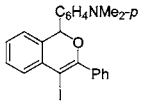
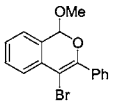
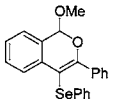
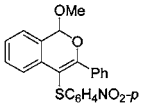
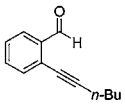
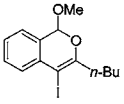
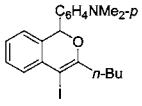
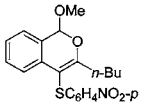
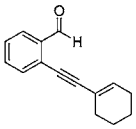
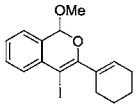
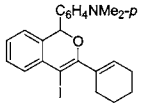
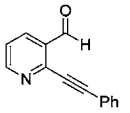
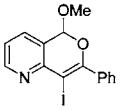
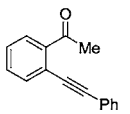
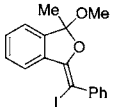
Interestingly, when we followed the stepwise procedure described in Barluenga's paper, we were unable to get high yields of the desired iodocyclization products. Instead, an unreactive solid, presumed to be the pyrilium salt, was generated. On the basis of this observation, a possible mechanism is proposed in Scheme 2. We believe that these cyclizations proceed by anti attack of the electrophile and

(9) For a recent review on multicomponent reactions, see, for instance: Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168.

(10) Tovar, J. D.; Swager, T. M. *J. Org. Chem.* **1999**, *64*, 6499.

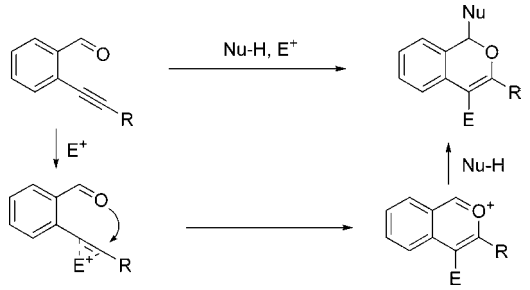
(11) (a) Sonogashira, K. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998; Chapter 5, pp 203−229. (b) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467.

Table 1. Electrophilic Cyclization of Acetylenic Aldehydes, Imines, and Ketones[a]

entry	carbonyl compound		nucleophile	electrophile	product		% isolated yield[b]
1		**1**	MeOH	I_2		**2**	93[c] (63-88)
2		**1**	*n*-BuOH	I_2		**3**	81
3		**1**		I_2		**4**	87
4		**1**		I_2		**5**	88 (45)
5		**1**	MeOH	NBS		**6**	51
6		**1**	MeOH	PhSeBr		**7**	65
7		**1**	MeOH	*p*-$NO_2C_6H_4SCl$		**8**	74
8		**9**	MeOH	I_2		**10**	84 (58-82)
9		**9**		I_2		**11**	70
10		**9**	MeOH	*p*-$NO_2C_6H_4SCl$		**12**	73
11		**13**	MeOH	I_2		**14**	81 (62-81)
12		**13**		I_2		**15**	83
13		**16**	MeOH	I_2		**17**	64
14		**16**	MeOH	ICl		**17**	64
15		**18**	MeOH	I_2		**19**	90 (21-48)

[a] All reactions were run under the following conditions, unless otherwise specified. To a solution of 2.5 mL of CH_2Cl_2 containing 0.25 mmol of the alkyne, 0.30 mmol of the nucleophile, and 0.25 mmol of K_2CO_3 was added 0.30 mmol of electrophile under stirring, and the resulting mixture was further stirred at room temperature for the desired time. [b] Barluenga's yields are reported in parentheses. [c] Reaction was run on a 1.0 mmol scale; the 0.25 mmol scale reaction provides an 88% yield of compound **2**.

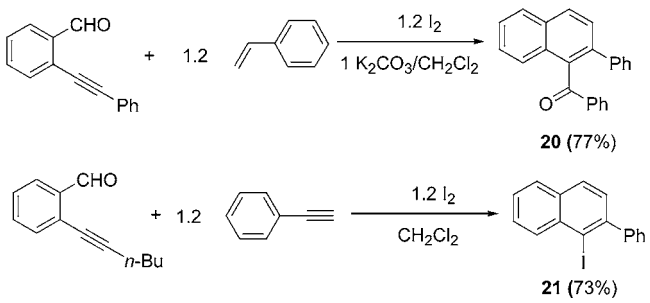
Scheme 2



the carbonyl to produce a pyrilium intermediate. Before it forms an insoluble precipitate,[10] the pyrilium intermediate is immediately trapped by the nucleophile present in the reaction mixture.

Our study has also shown that substituted naphthalenes can be synthesized in high yields by using alkenes or alkynes as the trapping reagent[12] (Scheme 3) and that the use of the

Scheme 3



more sophisticated iodonium reagent IPy_2BF_4 employed by Barluenga[12b] for this same process is not necessary. Once again, the use of readily available, easily handled I_2 greatly simplifies the procedure developed by Barluenga.

We believe that this approach to carbo- and heterocycles should prove to be quite useful in synthesis, particularly when one considers that there are many ways to transform the resulting halogen, sulfur, and selenium functional groups into other substituents. For instance, the resulting heterocyclic iodides should be particularly useful intermediates in many palladium-catalyzed processes such as Sonogashira,[11] Suzuki,[13] and Stille[14] cross-couplings and Heck reactions.[15]

Acknowledgment. We gratefully acknowledge the National Science Foundation and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research.

Supporting Information Available: Experimental procedures and characterization data for all starting materials and products. This material is available free of charge via the Internet at http://pubs.acs.org.

OL049690S

(12) (a) Asao, N.; Takahashi, K.; Lee, S.; Kasahara, T.; Yamamoto, Y. *J. Am. Chem. Soc*. 2002, *124*, 12650. (b) Asao, N.; Nogami, T.; Lee, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 10921. (c) Asao, N.; Kasahara, T.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2003**, *42*, 3504. (d) Barluenga, J.; Vazquez-Villa, H.; Ballesteros, A.; Gonzalez, J. M. *Org. Lett.* **2003**, *5*, 4121.

(13) (a) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147. (b) Lloyd-Williams, P.; Giralt, E. *Chem. Soc. Rev.* **2001**, *30*, 145. (c) Suzuki, A. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998; pp 49−97. (d) Miyaura, N. *Chem. Rev.* **1995**, *95*, 2457.

(14) (a) Negishi, E.; Dumond, Y. *Handbook of Organopalladium Chemistry for Organic Synthesis*; 2002; Vol. 1, p 767. (b) Kosugi, M.; Fugami, K. *Handbook of Organopalladium Chemistry for Organic Synthesis*; 2002; Vol. 1, p 263. (c) Kosugi, M.; Fugami, K. *J. Organomet. Chem.* **2002**, *653*, 50.

(15) (a) Crisp, G. T. *Chem. Soc. Rev.* **1998**, *27*, 427. (b) Brase, S.; De Meijere, A. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998; pp 99−166. (c) *Palladium Reagents in Organic Synthesis*; Heck, R. F., Ed.; Academic Press: San Diego, 1985; pp 276−287.