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Synthesis of Five- and Six-Membered Dihalogenated Heterocyclic Compounds by Electrophile-Triggered Cyclization

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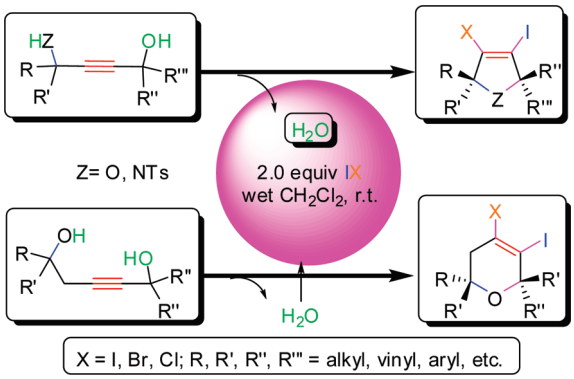
Received June 4, 2010



Highly substituted dihalogenated dihydrofurans, dihydropyrroles, and dihydro-2*H*-pyrans bearing alkyl, vinyl, aryl, and heteroaryl moieties can be prepared in good to excellent yields (up to 99%) by allowing 1,4-butyne-diol, 4-aminobut-2-yn-1-ol, and pent-2-yne-1,5-diol derivatives to react with different electrophiles (I_2, IBr, and ICl) at room temperature. Both halogen atoms generated from electrophiles were used effectively. The resulting halides can be further exploited by using palladium-catalyzed coupling reactions. The presence of trace amount of water is essential for this electrophilic cyclization.

Introduction

In past decades, the synthesis of heterocycles has continued to attract the interest of synthetic chemists due to the number of these compounds that show antidepressant, antihypertensive, and hypoglycemic activities as well as other biological effects.[1] Among these heterocycles, the five- and six-membered oxygenated or nitrogenated heterocycles are probably one of the most common structural subunits in numerous natural products. From simple to complex, these molecular frameworks are present in the structure of several biologically interesting compounds. In particular, dihydrofurans, dihydropyrroles, and dihydro-2*H*-pyrans are important intermediates for the synthesis of pharmaceuticals and biologically active molecules, such as lepadiformine,[2] nicotine,[3] phytane-type diterpenedilactones **3**−**7**,[4] citreoviral,[5] (+)-anamarine, and (+)-ambruticin[6] (Figure 1). Thus,

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Published on Web 07/23/2010 DOI: 10.1021/jo101085f
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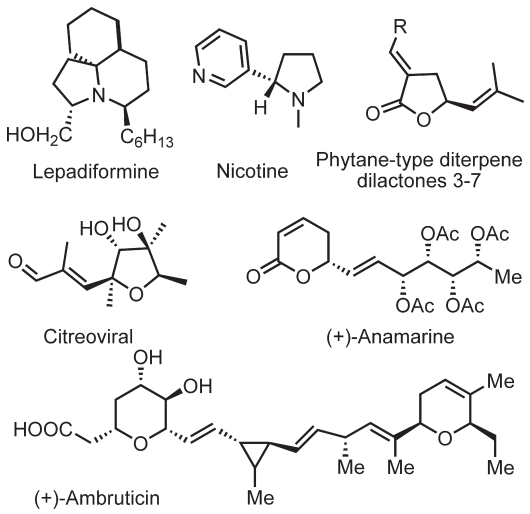
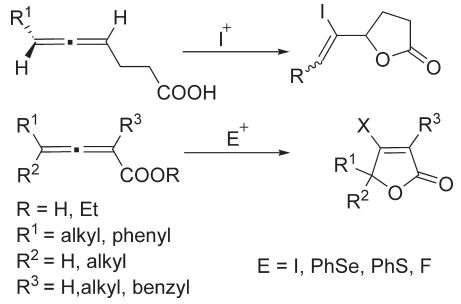


FIGURE 1. Some pharmaceuticals and biologically active molecules.

a mild, metal-free, environmently benign and atom economic protocol for the straightforward annulation of five- and six-membered heterocyclic rings is still of high demand.

In recent years, the electrophilic cyclization of heteroatomic nucleophiles, such as oxygen, nitrogen, and sulfur, with alkynes has proven to be an effective method for the synthesis of heterocyclic compounds.[7−25] We[7] and others have reported that the electrophilic cyclization[8] of alkynes can be a very powerful tool for the preparation of a wide variety of important heterocyclic compounds due to the mild, efficient, and clean reactions. Many important heterocycles, such as benzo[*b*]thiophenes,[9] benzofurans,[10] 2,3-dihydropyrroles and pyrroles,[11] furans,[7b,12] dihydropyrans,[7f,13] indoles,[14] isochromenes,[15] isocoumarins and α-pyrones,[16] isoquinolines and quinolines,[17] isoxazoles,[18] and oxazoles,[19] furanones,[20] furopyridines,[21] spiro[4,5]trienones,[22] coumestans and coumestrols,[23] naphthols,[24] and naphthalenes,[25] have been reported based on this strategy. Thus, electrophilic cyclization reactions continue to be an area of active research in the field of synthetic chemistry. However, the electrophilic cyclization of heteroatomic nucleophiles with allenes has often been considered to be synthetically less attractive due to the lack of efficient control of the regio- and stereoselectivity. Not long ago, Ma and co-workers reported an interesting cyclization of substituted allenoic acids in the presence of electrophiles to afford halogenated butenolides (Scheme 1).[26] So, the chemistry of allenes as organic synthons still needs to be explored more.

SCHEME 1



We found that 1,4-butyne-diol, 4-aminobut-2-yn-1-ol, and pent-2-yne-1,5-diol derivatives could isomerize to give the halogenated allene intermediates. These reactions are generally believed to proceed by a stepwise mechanism involving the allene cation intermediate formation in the presence of electrophiles, which can be readily trapped by nucleophiles (e.g., Cl, Br, I), then electrophilic activation of

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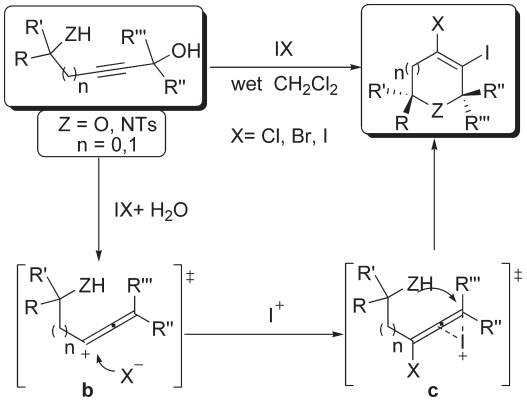
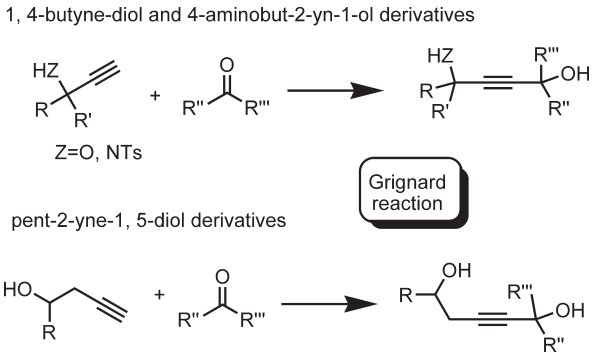
SCHEME 2. General Mechanism



SCHEME 3. Preparation of the Requisite Starting Materials



the carbon−carbon double bond of the halogenated allene intermediate followed by intramolecular nucleophilic attack on the cationic intermediate (Scheme 2).

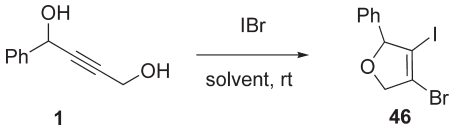
The success of this dihalogenation prompted us to establish the relative reactivity of various functional groups through cyclization.

Results and Discussion

This electrophilic cyclization has been applied to a variety of substrates, and the resulting products were characterized in order to determine the relative reactivities of various functional groups. The required starting materials are readily prepared from propargyl alcohol derivatives and aldehyde/ketone through the Grignard reaction (Scheme 3).

Initially, we started by using 0.3 mmol of 1-phenylbut-2-yne-1,4-diol **1** and 1.2 equiv of IBr in wet CH_2Cl_2 at room temperature; to our delight, the desired product 4-bromo-3-iodo-2-phenyl-2,5-dihydrofuran **46** was isolated in 55% yield after 6 h (Table 1, entry 1). When the amount of IBr was increased to 1.5 equiv, an 85% yield of **46** was obtained after 4 h (entry 2), and when the amount of IBr was added to 2 equiv, a 90% yield of **46** was obtained (entry 3). Surprisingly, increasing the amounts of IBr to 3 equiv gave a slightly decreased yield of 88% (entry 4). The reaction was also tested in dry CH_2Cl_2, but only a trace amount of **46** was observed, revealing the fact that protons are needed in this reaction system (entry 5). Hence, the effect of acids was then investigated in dried CH_2Cl_2. It was found that protic acids such as TsOH, TFA, TfOH, and $HSbF_6$ played an important role in this reaction, but no superior results were obtained (entries

TABLE 1. Optimization of Reaction Conditions[a]



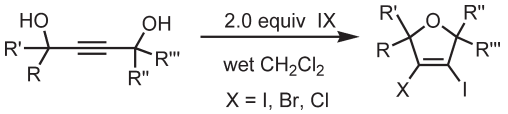
entry	solvent	IBr (equiv)	additive (equiv)	time (h)	yield (%)
1	CH_2Cl_2	1.2		6	55
2	CH_2Cl_2	1.5		4	85
3	**CH_2Cl_2**	**2.0**		**2**	**90**
4	CH_2Cl_2	3.0		2	88
5	dry CH_2Cl_2	2.0		12	trace
6	dry CH_2Cl_2	2.0	TsOH (1.0)	12	50
7	dry CH_2Cl_2	2.0	TFA (1.0)	2	38
8	dry CH_2Cl_2	2.0	TfOH (1.0)	2	mixture
9	dry CH_2Cl_2	2.0	$HSbF_6$ (1.0)	2	49
10	CH_2Cl_2	2.0	TsOH (1.0)	12	80
11	DCE	2.0		6	85
12	$CHCl_3$	2.0		2	80
13	MeOH	2.0		12	nr[b]
14	THF	2.0		12	40
15	1,4-dioxane	2.0		12	53
16	DMF	2.0		12	nr[b]
17	CH_3CN	2.0		12	66

[a]Conditions: 0.3 mmol of **1** with IBr in CH_2Cl_2 (2.0 mL) at room temperature. [b]No reaction.

6−9). When TsOH was used as an additive in wet CH_2Cl_2, no higher yield was obtained. With an attempt to optimize the yield of the product, we further studied the influence of different reaction media (entries 11−17). From the results obtained, it can be seen that DCE and $CHCl_3$ gave almost identical results, albeit with a very slightly lower yield. DMF and MeOH proved to be ineffective, whereas THF, 1,4-dioxane, and CH_3CN were less effective. With a series of detailed investigations mentioned above, the reaction conditions were eventually optimized as (entry 3): 1.0 equiv of **1** and 2.0 equiv of IBr in wet CH_2Cl_2 at room temperature.

To explore the scope of this electrophilic cyclization strategy, the reactions of **1** with different electrophiles (e.g., I_2, NIS, ICl, PhSeBr, and PhSeCl) have been studied under the optimized conditions. When using I_2 and ICl as the electrophilic reagents, the corresponding products **47** and **48** have been obtained in good to excellent yields (up to 99%). While using NIS, PhSeBr, and PhSeCl as the electrophilic reagents, no desired products were obtained. The other representative 1,4-butyne-diol derivatives were also subjected to the above conditions, as depicted in Table 2, and the corresponding products **49**−**77** were obtained in moderate to excellent yields. The reaction can tolerate a variety of functional groups at the *ortho*, *meta*, and *para* positions on the phenyl moiety of 1,4-butyne-diols, indicating that the steric effect had little impact on this transformation. The reaction works well with aromatic R groups (entries 7−21). Interestingly, it was found that substrate **5** with an *o*-$MeOC_6H_4$ group gave different products by changing the amount of IBr. When using 2 equiv of IBr as the electrophilic reagent, the corresponding product **55** was obtained in 55% after 4 h at room temperature (entry 13), whereas when the amount of IBr was decreased to 1.5 equiv, an 86% yield of **56** was obtained after 1 h at −25 °C (entry 14), showing the fact that **56** is formed first which then changes to **55** in the presence of IBr. A substrate such as **8** with different electrophiles (e.g., I_2, IBr) was also tested in this reaction. It was found that the yield of

TABLE 2. Synthesis of 3,4-Dihalogenated Dihydrofurans 46−77 from 1,4-Butyne-diol Derivatives 1−23[a]



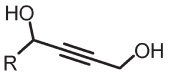
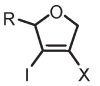
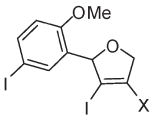
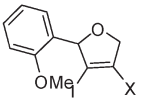
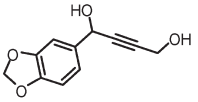
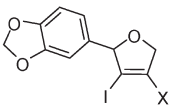
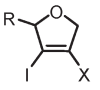
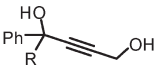
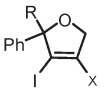
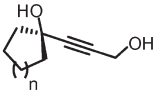
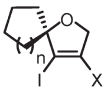
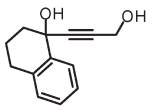
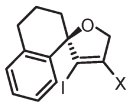
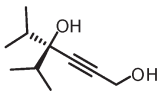
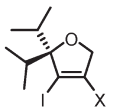
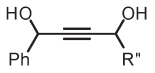
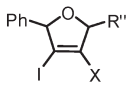
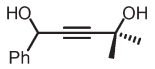
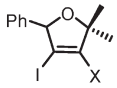
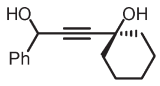
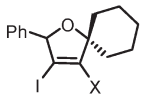
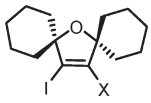
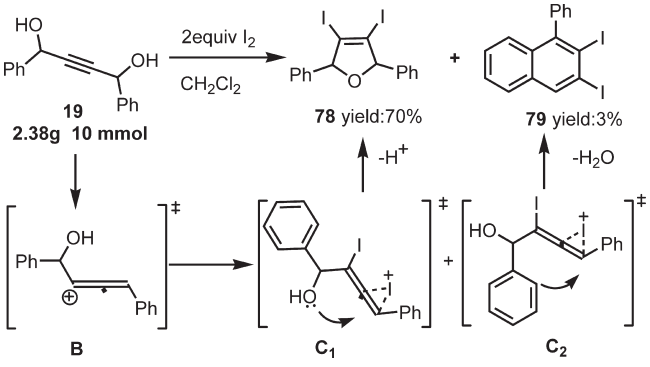
entry	substrate	electrophlie	product (s)	X	yield(%)	
1		**1** IBr		Br	**46**	90
2		I_2		I	**47**	99
3	R = Ph	NIS		I		0
4		ICl		Cl	**48**	75
5		PhSeBr		PhSe		0
6		PhSeCl		PhSe		0
7	R= *o*-MeC_6H_4	**2** IBr		Br	**49**	90
8	R= *o*-MeC_6H_4	I_2		I	**50**	86
9	R= *m*-MeC_6H_4	**3** IBr		Br	**51**	90
10	R= *p*-MeC_6H_4	**4** IBr		Br	**52**	86
11	R= *p*-$MeOC_6H_4$	IBr		Br	**53**	85
12	R= *o*-$MeOC_6H_4$	**5** I_2		I	**54**	90
13	R= *o*-$MeOC_6H_4$	IBr		Br	**55**	55
14	R= *o*-$MeOC_6H_4$	IBr[b]		Br	**56**	86
15		**6** IBr		Br	**57**	81
16	R= *m*-ClC_6H_4	**7** IBr		Br	**58**	99
17	R= *p*-ClC_6H_4	**8** I_2		I	**59**	70
18	R= *p*-ClC_6H_4	IBr		Br	**60**	87
19	R= *o*-FC_6H_4	**9** IBr		Br		0
20	R= 2-(naphthalen-2-yl)	**10** IBr		Br	**61**	85
21	R= 2-(naphthalen-2-yl)	I_2		I	**62**	92
22	R= furan	**11** IBr		Br	**63**	80
23	 R = CH_3	**12** IBr		Br	**64**	94
24	R = Ph	**13** IBr		Br	**65**	85
25	 n = 0	**14** IBr[c]		Br	**66**	86
26	n = 1	**15** IBr[c]		Br	**67**	97
27	n = 2	**16** IBr[c]		Br	**68**	87
28	n = 2	I_2[c]		I	**69**	82

TABLE 2. Continued

entry	substrate	electrophlie	product (s)	X	yield(%)	
29		**17** IBr		Br	**70**	80
30		I_2		I	**71**	99
31		**18** IBr[c]		Br	**72**	85
32	 R"=Ph	**19** IBr		Br	**73**	90
33	R"= C_3H_7	**20** IBr		Br	**74**	81
34		**21** I_2		I	**75**	91
35		**22** I_2		I	**76**	88
36		**23** I_2[c]		I	**77**	82

[a]All reactions were run under the following conditions, unless otherwise indicated: 0.30 mmol of 1,4-butyne-diols and 2.0 equiv of electrophiles in 3 mL of solvent were stirred at room temperature. [b]With 0.3 mmol of **5** with 1.5 equiv of IBr in CH_2Cl_2 (3.0 mL) at −25 °C for 1 h. [c]The reaction was carried out at 40 °C.

SCHEME 4



corresponding product **60** was better than **59**, which might be due to the fact that the reactivity of IBr is higher than I_2 (entries 17 and 18). 1,4-Butyne-diol possessing a heterocyclic ring, such as a furan nucleus, can also afford the desired product **63** in 80% yield (entry 22). Substrates such as **14**−**18** with aliphatic groups can also give corresponding dihalogenated heterocyclic compounds **66**−**72** in good to excellent yields (entries 25−31). Other substrates such as **19**−**23** can also afford corresponding products **73**−**77** in good yield (entries 32−36).

Much more important from the viewpoint of industrial preparation was our investigation about the reaction of 10 mmol (2.38 g) of 1,4-diphenylbut-2-yne-1,4-diol **19** in the presence of **2** equiv of I_2; fortunately, 3,4-diiodo-2,5-diphenyl-2,5-dihydrofuran **78** was obtained in 70% yield after 2 h,

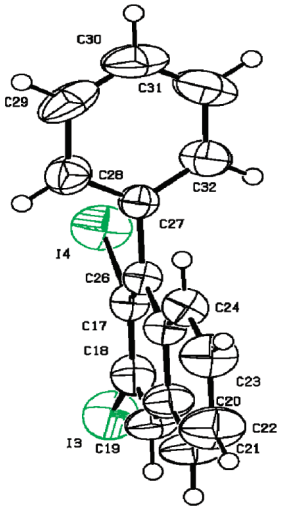
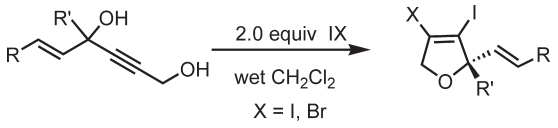


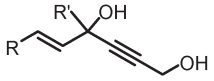
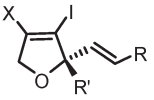
FIGURE 2. Structure of **79**.

along with 2,3-diiodo-1-phenylnaphthalene **79** (3% yield), confirming the existence of the intermediates $\mathbf{C_1}$ and $\mathbf{C_2}$ (Scheme 4). The molecular structure of the representative product **79** was determined by X-ray crystallography (Figure 2).

Furthermore, to expand the scope of this reaction, we also investigated a range of 5-en-2-yne-1,4-diol derivatives **24**−**26**, and it was found that substrates **24**−**26** were converted into 3,4-dihalogenated-2-vinyl-2,5-dihydrofurans **80**−**84** in moderate to good yield, as depicted in Table 3. Noteworthy,

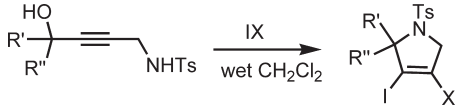
TABLE 3. Synthesis of 3,4-Dihalogenated 2-Vinyl-2,5-dihydrofuran from 5-En-2-yne-1,4-diol Derivatives 24−26[a]

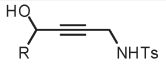
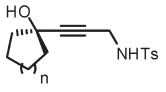
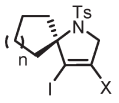
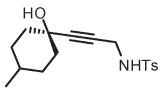
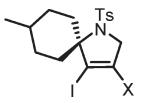
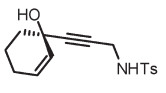
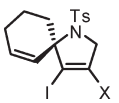


entry	substrate	electrophlie		product (s)	X	yield (%)	
37		**24**	I_2		I	**80**	82
38			IBr [b]		Br	**81**	76
	R=Ph, R'=H						
39	R=Me, R'=H	**25**	I_2		I	**82**	55
40	R=Me, R'=H		IBr [b]		Br	**83**	33
41	R=Ph, R'= Me	**26**	I_2		I	**84**	82

[a]All reactions were run under the following conditions, unless otherwise indicated: 0.30 mmol of 5-en-2-yne-1,4-diols and 2.0 equiv of electrophiles in 3 mL of solvent were stirred at 0 °C. [b]The reaction was carried out at −10 °C.

TABLE 4. Synthesis of 3,4-Dihalogenated Dihydropyrroles[a]



entry	substrate	electrophlie		product (s)		yield (%)	
					X		
42	R = Ph	**27**	IBr		Br	**85**	82
43			ICl		Cl	**86**	75
44			I_2		I	**87**	86
45	R = *m*-MeC_6H_4	**28**	IBr		Br	**88**	87
46	R = *m*-$MeOC_6H_4$	**29**	IBr		Br	**89**	80
47		**30**	IBr[b]		Br	**90**	80
	n = 0						
48	n = 1	**31**	IBr[b]		Br	**91**	89
49	n = 2	**32**	IBr[b]		Br		mixture
50	n = 2		I_2[b]		I	**92**	45
51	n = 3	**33**	IBr[b]		Br	**93**	85
52		**34**	IBr[b]		Br	**94**	84
53		**35**	I_2[b]		I	**95**	70

[a]All reactions were run under the following conditions, unless otherwise indicated: 0.30 mmol of 4-aminobut-2-yn-1-ols and 2.0 equiv of electrophiles in 3 mL of solvent were stirred at room temperature. [b]The reaction was carried out at 40 °C.

the double bond was retained in this reaction, which provides ways for further transformations.

Additionally, various representative 4-aminobut-2-yn-1-ol derivatives were also investigated in this reaction. It was found that, under the optimized conditions, substrates **27**−**35** were converted into 3,4-dihalogenated dihydropyrroles **85**−**95** in moderate to excellent yield, as depicted in Table 4. The behavior of substrate *N*-(4-hydroxy-4-phenylbut-2-ynyl)-4-methylbenzenesulfonamide **27** with different electrophiles (e.g., IBr, ICl, and I_2) was investigated in this reaction; to our delight, the corresponding 3,4-dihalogenated dihydropyrroles **85**−**87** were obtained in 75−86% yield (Table 4, entries 42−44). To further confirm the structural assignment of products, the relative configuration of the product **89** was unambiguously assigned by X-ray crystallography (Figure 3). Interestingly, substrates such as **30**−**34** with aliphatic groups also gave corresponding dihalogenated heterocyclic compounds **90**−**94** in moderate to good yield (entries 47−52). Other substrate such as **35** can also be converted into corresponding product **95** in 70% yield, with double bonds retained.

Since the first preparation of indole by Baeyer in 1866,[27] its chemistry has been extensively investigated as a consequence of its prevalence in the structures of many biologically active natural products, including some useful drugs.[27,28] Due to its special characteristic, we also prepared the indole derivatives **36** and **37**, and it was found that, under the optimized conditions, the corresponding dihalogenated indole heterocyclic compounds **96** and **97** were obtained in 72−76% yield (Scheme 5).

Due to the wide occurrence of six-membered pyran rings as key structural subunits in numerous natural products, such as (+)-ambruticin and others,[6] the straightforward annulation of pyran rings is still needed. Under the optimized conditions, we also investigated pent-2-yne-1,5-diol derivatives **54**−**67**; fortunately, the corresponding dihalogenated pyran rings **98**−**111** were also obtained in moderate yield, as depicted in Table 5. From these results, it can be seen that this reaction works well with aromatic groups (Table 5, entries 54−59). Electron-rich aryl groups showed better results than those with an electron-withdrawing group in this tandem reaction (**39** vs **40**). With different electrophiles (e.g., I_2, IBr, and ICl), substrate **41** with a styrene group can also afford the desired products **104**−**106** in 72, 83, and 20% yield, respectively (entries 60−62). Substrate such as **45** with aliphatic groups also gave corresponding spiro skeletons **107**−**111** in moderate yield (entries 63−67).

A standard feature of this process is the fact that the dihalogenated heterocyclic compounds produced by electrophiles (e.g., I_2, IBr, and ICl) can be further exploited by using various palladium-catalyzed processes. For example, the Sonagashira coupling,[29] Suzuki coupling,[30] and Heck coupling[31] of 3,4-diiodo-dihydrofuran **78** afforded the corresponding disubstituted products **111**−**113** in moderate to good yield. The dihydrofuran **78** can be oxidized to 3,4-diiodo-2,5-diphenylfuran **114** by 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) (Scheme 6).

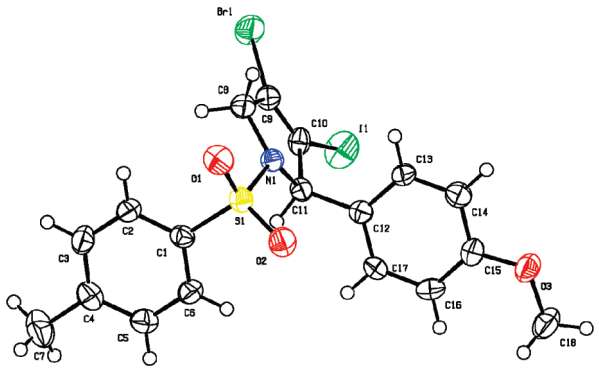


FIGURE 3. Structure of **89**.

In a similar manner, the Sonogashira coupling of 3-bromo-4-iodo-2,5-diphenyl-2,5-dihydrofuran **73** with phenylacetylene gave disubstituted alkyne **111** in 92% yield, whereas the reaction of 4-chloro-3-iodo-2-phenyl-1-tosyl-2,5-dihydro-1*H*-pyrrole **86** with phenylacetylene afforded monosubstituted alkyne **115**, and only the iodine atom was involved in the palladium-catalyzed Sonogashira coupling reaction (Scheme 7).

Conclusions

Highly substituted dihalogenated dihydrofurans, dihydropyrroles, and dihydro-2*H*-pyrans have been obtained in moderate to excellent yields from simple starting materials by the electrophilic cyclization of 1,4-butyne-diols, 4-aminobut-2-yn-1-ols, and pent-2-yne-1,5-diols by electrophiles (I_2, IBr, and ICl), during which several C−X (O, N, Cl, Br, I) bonds were formed. This method tolerates many alkyl, vinyl, aryl, and heteroaryl functional groups. Both halogen atoms generated from electrophiles were used effectively. The dihalogenated moiety can be readily introduced into the heterocycle in a position not easily obtained previously. Subsequent functionalization of the resulting heterocycles by palladium-catalyzed coupling reactions leads to a number of interesting five- and six-membered substituted skeletons. In addition, the presence of a trace amount of water is needed for this electrophilic cyclization.

Experimental Section

General Procedure A: Synthesis of 1,4-Butyne-diol Derivatives. To a stirred solution of the propargyl alcohol (10 mmol) in THF was added ethylmagnesium bromide (20 mmol) at room temperature. The resulting solution was refluxed for 1 h at 80 °C. Then aldehyde (1.0 equiv) in THF (0.35 M) was added slowly by

(27) (a) Baeyer, A. *Justus Liebigs Ann. Chem.* **1866**, *140*, 295. For historical overviews of indole chemistry, see: (b) Julian, P. L.; Meyer, E. W.; Printy, H. C. In *Heterocyclic Compounds*; Elderfield, R. C, Eds.; Wiley: New York, 1952; Vol. 3, pp 1−274. (c) Sundberg, R. J. *The Chemistry of Indoles*; Academic Press: New York, 1970. (d) Sundberg, R. J. *Indoles* Academic Press: London, 1996.

(28) Brancale, A.; Silvestri, R. *Med. Res. Rev.* **2007**, *27*, 209.

(29) For reviews, see: (a) Campbell, I. B. The Sonogashira Cu−Pd-Catalyzed Alkyne Coupling Reaction. In *Organocopper Reagents*; Taylor, R. T. K., Ed.; IRL Press: Oxford, UK, 1994; pp 217−235. (b) Sonogashira, K.; Takahashi, S. *Yuki Gosei Kagaku Kyokaishi* **1993**, *51*, 1053. (c) Sonogashira, K. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 3, pp 521−549.

(30) For reviews, see: (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147. (c) Suzuki, A. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 1998; Chapter 2.

(31) For leading reviews of the Heck reaction, see: (a) De Meijere, A.; Meyer, F. E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2379. (b) Shibasaki, M.; Boden, C. D. J.; Kojima, A. *Tetrahedron* **1997**, *53*, 7371. (c) Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, *28*, 2. (d) Overman, L. E. *Pure Appl. Chem.* **1994**, *66*, 1423.

SCHEME 5. Synthesis of Dihalogenated Indole Derivatives 96 and 97

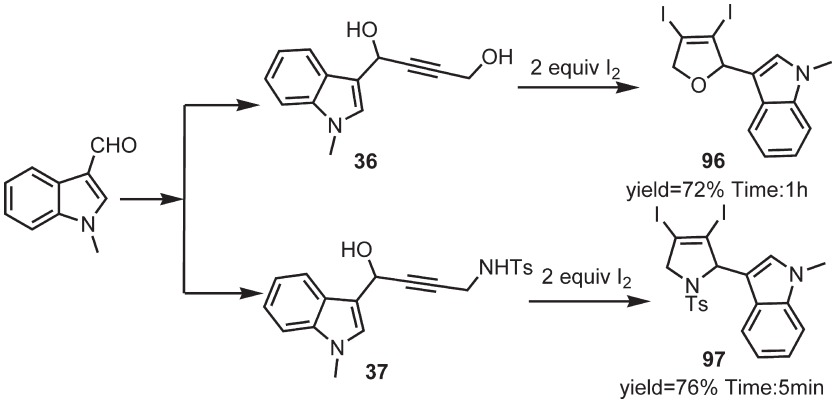
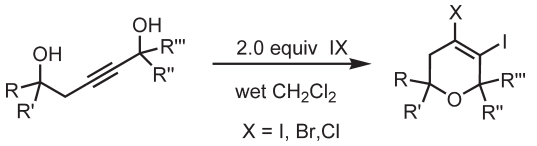
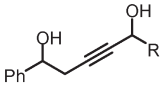
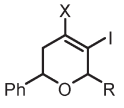
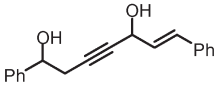
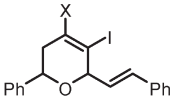
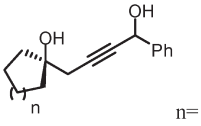
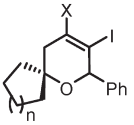
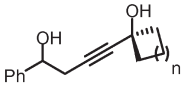
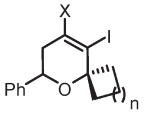


TABLE 5. Synthesis of 4,5-Dihalogenated 3,6-Dihydro-2*H*-pyran[a]



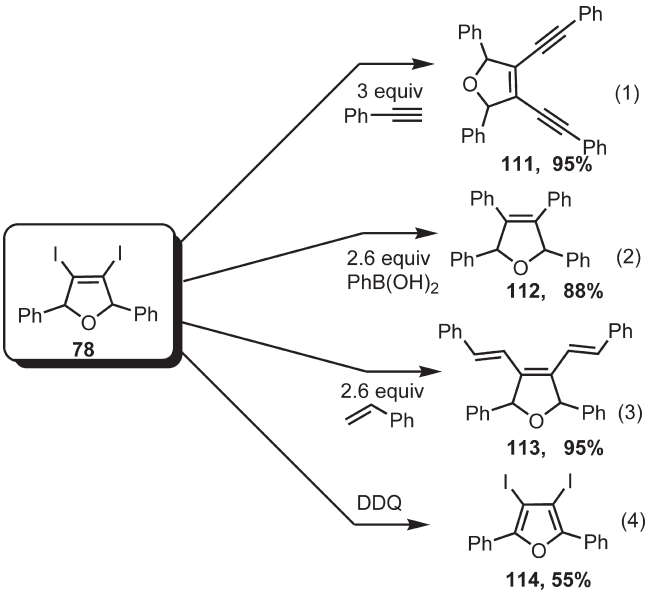
entry	substrate		electrophlie		product (s)		yield (%)	
						X		
54	R = Ph	**38**	IBr			Br	**98**	75
55			I_2			I	**99**	76
56	R = *m*-MeC_6H_4	**39**	IBr			Br	**100**	75
57	R = *m*-MeC_6H_4		I_2			I	**101**	80
58	R = *m*-ClC_6H_4	**40**	IBr			Br	**102**	44
59	R = *m*-ClC_6H_4		I_2			I	**103**	40
60		**41**	I_2			I	**104**	72
61			IBr[b]			Br	**105**	83
62			ICl[b]			Cl	**106**	20
63	 n=1	**42**	I_2			I	**107**	74
64	n=2	**43**	I_2			I	**108**	78
65	 n =0	**44**	I_2			I	**109**	70
66	n =1	**45**	I_2			I	**110**	55

[a]All reactions were run under the following conditions, unless otherwise indicated: 0.30 mmol of pent-2-yne-1,5-diols and 2.0 equiv of electrophiles in 3 mL of solvent were stirred at room temperature. [b]The reaction was carried out at −10 °C.

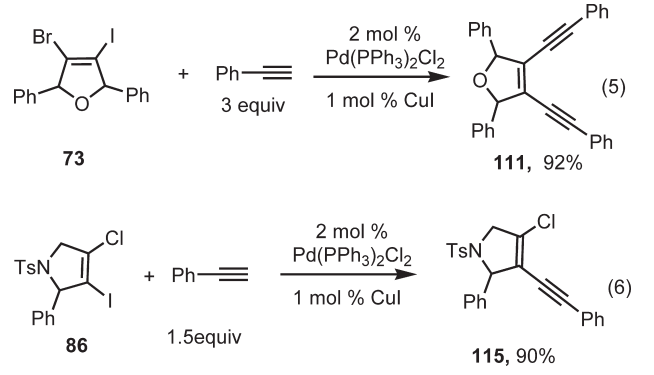
syringe to the resulting solution at room temperature and stirred for 3 h. The reaction mixture was quenched by addition of saturated aqueous ammonium chloride (40 mL) and extracted with ethyl ether (2 × 40 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was purified by flash column chromatography to obtain the pure 1,4-butyne-diol derivatives.

1-Phenylbut-2-yne-1,4-diol (1): solid, mp 83−85 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.54 (dd, J = 7.8, 1.2 Hz, 2H),

SCHEME 6



SCHEME 7. Palladium-Catalyzed Sonogashira Coupling Reaction



7.41−7.32 (m, 3H), 5.49 (d, J = 5.7 Hz, 1H), 4.32 (dd, J = 6.0, 1.2 Hz, 2H), 2.87 (d, J = 5.7 Hz, 1H), 2.34 (t, J = 5.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 140.3, 128.6, 128.5, 126.6, 85.5, 84.9, 64.5, 51.0; IR (neat, cm^{-1}) 1643, 1450, 1291, 1118, 1020, 692; HRMS (ESI) calcd for $C_{10}H_{10}O_2M + H$ = 163.0754, found 163.0758.

General Procedure B: Synthesis of 3,4-Dihalogenated 2,5-Dihydrofuran Derivatives. To a solution of **1** (0.30 mmol) in wet CH_2Cl_2 (3.0 mL) was added 0.6 mmol, 2 equiv of electrophiles (I_2, IBr, and ICl) at room temperature. When the reaction was considered complete as determined by TLC analysis, the reaction mixture was extracted with ethyl ether (40 mL), washed with water and saturated brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by chromatography on silica gel to afford corresponding dihalogenated heterocyclic compounds.

4-Bromo-3-iodo-2-phenyl-2,5-dihydrofuran (46). Compound **46** was isolated in 90% yield following the general procedure B: reaction time = 4 h; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.42−7.32 (m, 5H), 5.61 (dd, J = 5.4, 3.9 Hz, 1H), 4.87 (dd, J = 12.3, 6.0 Hz, 1H), 4.76 (dd, J = 12.3, 3.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 138.7, 128.9, 128.5, 127.5, 125.2, 97.2, 93.2, 78.7; IR (neat, cm^{-1}) 1776, 1616, 1453, 1042, 753, 696; HRMS (ESI) calcd for $C_{10}H_8BrIO$ M + NH_4 = 367.9141, found 367.9150.

General Procedure C: Synthesis of 3,4-Dihalogenated 2-Vinyl-2,5-dihydrofurans 80−84. To a solution of **24** (0.30 mmol) in wet CH_2Cl_2 (3.0 mL) was added 0.6 mmol, 2 equiv of electrophiles IBr at −10 °C; 0.5 h later, the reaction was considered complete as determined by TLC analysis, and the reaction mixture was extracted with ethyl ether (40 mL), washed with water and saturated brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by chromatography on Al_2O_3 to afford corresponding dihalogenated heterocyclic compound **81**.

(*E*)**-4-Bromo-3-iodo-2-styryl-2,5-dihydrofuran 81.** Compound **81** was isolated in 76% yield as an oil following the general procedure C: reaction time = 0.5 h; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.41 (d, J = 7.2 Hz, 2H), 7.34−7.28 (m, 3H), 6.69 (d, J = 15.6 Hz, 2H), 6.09 (dd, J = 16.0, 8.0 Hz, 1H), 5.25−5.20 (m, 1H), 4.73−4.66 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 135.9, 134.5, 128.6, 128.2, 126.9, 126.2, 125.3, 96.1, 92.2, 78.2; IR (neat, cm^{-1}) 1075, 1449, 1360, 1220, 1061, 696; HRMS (ESI) calcd for $C_{12}H_{10}BrIO$ M + NH_4 = 393.9298, found 393.9302.

General Procedure D: Synthesis of 3,4-Dihalogenated Dihydropyrroles. To a solution of 4-aminobut-2-yn-1-ol derivatives **27−35** (0.30 mmol) in wet CH_2Cl_2 (3.0 mL) was added 0.6 mmol, 2 equiv of electrophiles at room temperature. When the reaction was considered complete as determined by TLC analysis, the reaction mixture was extracted with ethyl ether (40 mL), washed with water and saturated brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by chromatography on silica gel to afford corresponding 3,4-dihalogenated dihydropyrroles **85−95**.

4-Bromo-3-iodo-2-phenyl-1-tosyl-2,5-dihydro-1*H*-pyrrole 85. Compound **85** was isolated in 82% yield as a solid following the general procedure D: reaction time = 3 h; mp 124−126 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.43 (d, J = 8.0 Hz, 2H), 7.32−7.29 (m, 3H), 7.20−7.17 (m, 4H), 5.42 (dd, J = 5.6, 2.4 Hz, 1H), 4.50 (dd, J = 14.0, 2.4 Hz, 1H), 4.34 (dd, J = 13.6, 2.4 Hz, 1H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 143.7, 137.8, 134.8, 129.6, 128.6, 128.5, 128.0, 127.1, 123.1, 98.1, 76.1. 59.4, 21.5; IR (neat, cm^{-1}) 1347, 1160, 1093, 1042, 818, 672, 579; HRMS (ESI) calcd for $C_{17}H_{15}BrINO_2S$ M + H = 503.9124, found 503.9128.

General Procedure E: Synthesis of 4,5-Dihalogenated 3,6-Dihydro-2*H*-pyrans 98−110. To a solution of pent-2-yne-1,5-diol derivatives **54−67** (0.30 mmol) in wet CH_2Cl_2 (3.0 mL) was added 0.6 mmol, 2 equiv of electrophiles at room temperature. When the reaction was considered complete as determined by TLC analysis, the reaction mixture was extracted with ethyl ether (40 mL), washed with water and saturated brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by chromatography on silica gel to afford corresponding 4,5-dihalogenated 3,6-dihydro-2*H*-pyrans **98−110**.

4-Bromo-5-iodo-2,6-diphenyl-3,6-dihydro-2*H*-pyran 98. Compound **98** was isolated in 75% yield following the general procedure E: reaction time = 4 h; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.44−7.20 (m, 10H), [5.54(s), 5.31 (dd, J = 3.2, 1.8 Hz), 1H], [4.92 (dd, J = 10.4, 2.8 Hz), 4.91 (dd, J = 8.8, 5.2 Hz), 1H], 3.15−2.89 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 140.3, 140.0, 139.9, 137.1, 129.5, 128.8, 128.8, 128.7, 128.7, 128.5, 128.4, 128.4, 128.3, 128.0, 127.9, 127.8, 125.8, 125.8, 106.1, 100.7, 86.3, 84.3, 77.1, 69.7, 45.6, 44.5; IR (neat, cm^{-1}) 1614, 1438, 1361, 1218, 1065, 816, 743, 552; HRMS (ESI) calcd for $C_{17}H_{14}BrIO$ M + NH_4 = 457.9611, found 457.9618.

Acknowledgment. We thank the NSF (NSF-20732002, NSF-2087205, NSF-20090443) and the Fundamental Research Funds for the Central Universities for financial support.

Supporting Information Available: Detailed experimental procedure and copies of ^{1}H NMR and ^{13}C NMR spectra of all compounds, and X-ray data of **79** and **89** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.