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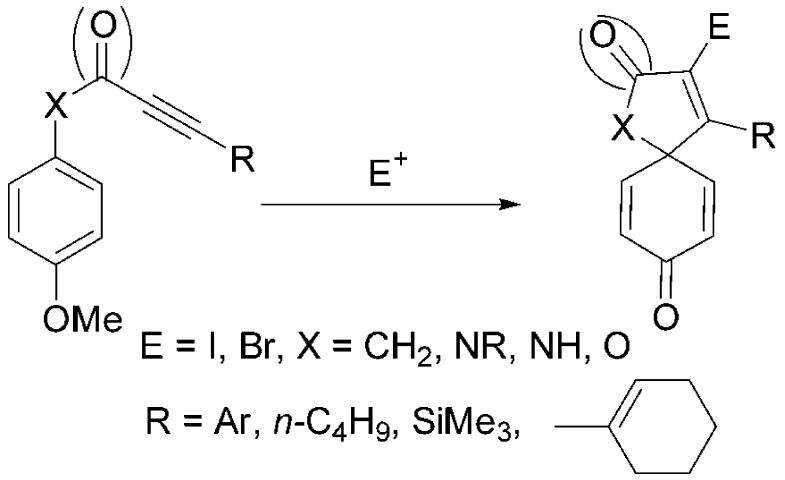

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Synthesis of Spiro[4.5]trienones by Intramolecular *ipso*-Halocyclization of 4-(*p*-Methoxyaryl)-1-alkynes

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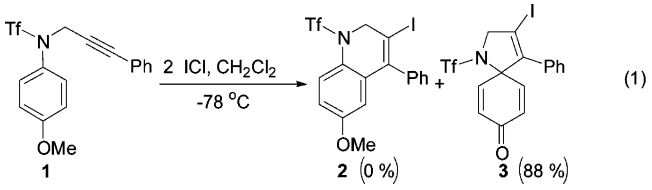
Annulated arene heterocycles and carbocycles can be conveniently prepared by the electrophilic cyclization of arenes bearing heteroatom- or carbon-tethered olefins, respectively.[1] However, only a few examples of the analogous chemistry of alkynes have been reported, although this would appear to be a very efficient route to a wide range of useful, functionally substituted heterocycles and carbocycles.[2] All previously reported reactions of this type have employed *ortho*-substituted arenes. We wish to report a very useful route to spiro[4.5]trienones via intramolecular *ipso*-halocyclization of simple methoxy-substituted 4-aryl-1-alkynes.

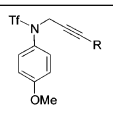
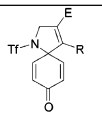
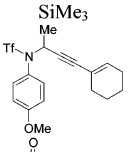
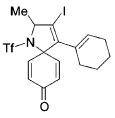
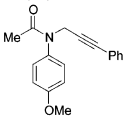
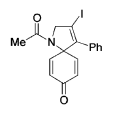
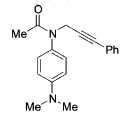
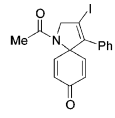
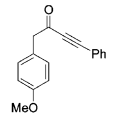
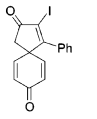
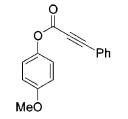
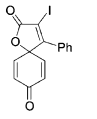
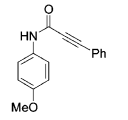
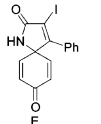
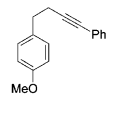
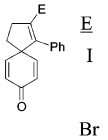
During our study of the cyclization of simple *N*-propargylic anilines to quinolines,[2d] we had occasion to examine the reaction of *N*-(4-methoxyphenyl)-*N*-(3-phenyl-2-propyn-1-yl)triflamide (**1**) with 2 equiv of ICl in CH_2Cl_2 at −78 °C for 0.5 h (Conditions A). To our surprise, the 1-azaspirotrienone **3** was produced exclusively in an 88% yield and none of the expected dihydroquinoline **2** was observed (eq 1 and Table 1, entry 1).[3] This is a rare example of an iodonium ion-induced intramolecular *ipso*-cyclization of an alkyne onto an arene under extremely mild reaction conditions.[4] Since the spiro[4.5]decane skeleton is a key structural feature present in a number of interesting natural products,[5] this process represents a powerful new tool for the synthesis of such compounds, which may be difficult to prepare by any other present method.[6] We therefore chose to study this cyclization in more detail.



When the cyclization of **1** was performed at room temperature, the spirotrienone **3** was obtained in only a 46% yield together with a 48% yield of **2**. This suggests that *ipso*-cyclization is a kinetically favored process. The corresponding *N*-acetyl derivative **15** also cyclized efficiently at −78 °C to produce spiroamide **16** in a 66% yield (Table 1, entry 9). However, analogous anilines with the acetyl group replaced by a hydrogen or methyl group failed to generate the corresponding *ipso*-cyclization products. In these two cases, the presence of electron-releasing groups on the nitrogen facilitated electrophilic aromatic substitution *ortho* to the nitrogen to produce the corresponding quinolines.[2d]

ICl proved to be an efficient electrophile for this and a number of related spirocyclizations, as indicated in Table 1 (entries 1 and 4−8). The reaction accommodates various substituents at the remote end of the triple bond of the *N*-triflanilide. Electron-rich or electron-poor aryl- and alkyl-substituted alkynes (entries 4−6) are readily accommodated, producing the expected spirocyclic products in good yields. The presence of a sterically hindered silyl group presents no difficulty, and the reaction proceeds without desilylation,

Table 1. Synthesis of Spirotrienones by the Reaction of Arylalkynes and Halogen Electrophiles

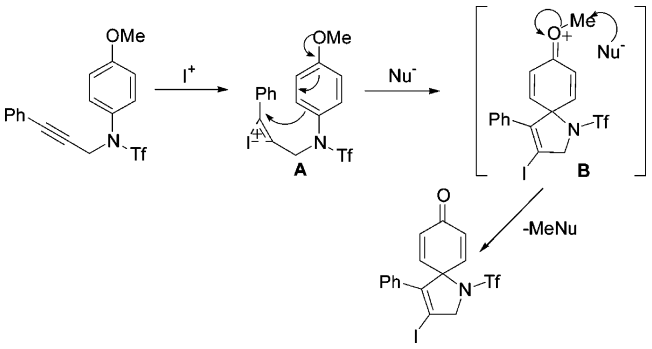
entry	arylalkyne[a]		E^+	cond.[b]	time (min)	product		% yield
								
	R					E		
1	Ph	**1**	ICl	A	30	I	**3**	88
2	Ph		I_2	B	120	I		90
3	Ph		Br_2	B	10	Br	**4**	92
4	*p*-$MeOC_6H_4$	**5**	ICl	A	10	I	**6**	84
5	*p*-AcC_6H_4	**7**	ICl	A	30	I	**8**	89
6	*n*-Bu	**9**	ICl	A	10	I	**10**	75
7	$SiMe_3$	**11**	ICl	A	30	I	**12**	58[c]
8		**13**	ICl	A	10		**14**	83
9		**15**	ICl	A	10		**16**	66[d]
10		**17**	ICl	A	30		**16**	61
11		**18**	I_2	B	10		**19**	98
12		**20**	I_2	B	60		**21**	100
13		**22**	I_2	B	720		**23**	84
14		**24**	ICl	C	10	 E I	**25**	93
15			Br_2	C	10	Br	**26**	98

[a] All reactions were run on a 0.3 mmol scale. [b] See the text and Supporting Information for Conditions A−C. [c] Three equivalents of ICl was required. [d] Four equivalents of ICl was required.

although 3 equiv of ICl was required to get a good yield (entry 7).[7] The presence of an olefin on the end of the triple bond presented no difficulties (entry 8). We were also pleased to see that the *p*-methoxy group in acetanilide **15** could be replaced by a

10.1021/ja053079m CCC: $30.25

Scheme 1

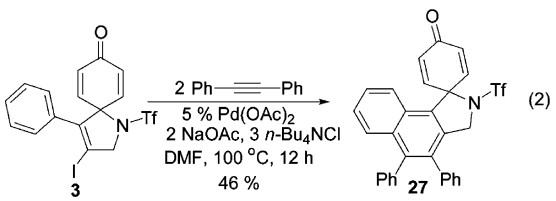


p-dimethylamino group, and spirotrienone **16** was obtained in a comparable yield after acid hydrolysis (entry 10).

I_2 has also successfully been employed in this process as an electrophile. When **1** was initially treated with 2 equiv of I_2 in MeCN at room temperature, dihydroquinoline **2** was obtained in an 80% yield without any formation of spirotrienone **3**. Interestingly, by simply adding 2 equiv of $NaHCO_3$ (Conditions B), spirotrienone **3** can be formed in a 90% yield in 2 h, although a longer reaction time was required than when ICl was employed (entry 2). It is noteworthy that, by this minor modification in the reaction conditions, we can switch the *ipso*/*ortho* cyclizations "on" or "off" at will. Bromo-substituted spirotrienone **4** was also obtained in an excellent yield under similar *ipso* reaction conditions when Br_2 was employed as the electrophile (entry 3).

The synthetic utility of this process would be greatly increased if we could vary the nature of the substitution between the alkyne and the arene. We have, in fact, been able to replace the nitrogen moiety by a ketone, ester, or amide moiety and still obtain excellent yields using reaction Conditions B (entries 11−13). The reaction with a ketone linkage is substantially faster than that with the corresponding amide (10 min versus 12 h). With an ethane linkage, careful optimization of the reaction conditions indicated that the reaction temperature, the base, and the presence of a protic solvent are all crucial for the success of the reaction. Thus, when 4-(4-methoxyphenyl)-1-phenyl-1-butyne was treated with 5 equiv of electrophile and 2 equiv of NaOMe in a mixed solvent system of 3:4 CH_2Cl_2/MeOH at −78 °C (Conditions C), iodo- (**25**) and bromotrienone (**26**) were obtained in almost quantitative yields.

These halogen-promoted aromatic cyclizations not only quickly construct a complex, highly functionalized carbon skeleton but also provide a very useful handle for further structural manipulation. For example, the iodospirotrienone **3** produced by this strategy can be employed in palladium-catalyzed reactions, such as the carboannulation of alkynes,[8] to quickly achieve additional molecular complexity (eq 2).



(2)

A tentative mechanistic interpretation to explain the formation of the spirotrienone might reasonably assume an initial interaction of electrophilic iodine with the alkyne residue to give the iodonium intermediate **A** (Scheme 1). **A** can then undergo intramolecular *ipso*-attack on the electron-rich aromatic ring to form intermediate **B**. The methyl group of **B** is removed via nucleophilic displacement by the X^-, HCO_3^- (Conditions B), or MeO^- (Conditions C) present in the reaction mixture.

In summary, a simple, very versatile new approach to a wide variety of 3-halospirotrienones bearing a spiro[4.5]decane ring system has been developed. The reaction proceeds under very mild conditions and tolerates considerable functionality. A systematic study of the reaction has revealed that different "optimal" reaction conditions are required for different substrates and electrophiles. Further work to better understand the effect of the base and the solvent on the reaction path and utilization of these spirotrienones as pivotal intermediates in the preparation of biologically active compounds is presently underway.

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

References

(1) (a) Barluenga, J.; González, J. M.; Campos, P. J.; Asensio, G. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 319−320. (b) Barluenga, J.; González, J. M.; Campos, P. J.; Asensio, G. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1546−1567. (c) Barluenga, J.; Trincado, M.; Rubio, E.; González, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 3416−3417.

(2) (a) Kitamura, T.; Takachi, T.; Kawasato, H.; Taniguchi, H. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1969−1973. (b) Klein, T. R.; Bergemann, M.; Yehia, N. A. M.; Fanghänel, E. *J. Org. Chem.* **1998**, *63*, 4626−4631. (c) Yao, T.; Marino, M. A.; Larock, R. C. *Org. Lett.* **2004**, *6*, 2677−2680. (d) Zhang, X.; Campo, M. A.; Yao, T.; Larock, R. C. *Org. Lett.* **2005**, *7*, 763−766.

(3) For Lewis acid promoted intra- or intermolecular reactions of 4-methoxyarenes with alkynes, see: (a) Haack, R. A.; Beck, K. R. *Tetrahedron Lett.* **1989**, *30*, 1605−1608. (b) Nagao, Y.; Lee, W. S.; Jeong, I.; Shiro, M. *Tetrahedron Lett.* **1995**, *36*, 2799−2802. (c) Citterio, A.; Sebastiano, R.; Maronati, A.; Santi, R.; Bergamini, F. *Chem. Commun.* **1994**, 1517−1518. (d) Boyle, F. T.; Hares, O.; Matusiak, Z. S.; Li, W.; Whiting, D. A. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2707−2711. (e) Boyle, F. T.; Hares, O.; Matusiak, Z. S.; Li, W.; Whiting, D. A. *Chem. Commun.* **1990**, 518−519.

(4) The *ipso* cyclization of bis(4-methoxybenzylthio)acetylene by ICl has been reported, but the scope of this cyclization has not yet been examined. See: Appel, T. R.; Yehia, N. A. M.; Baumeister, U.; Hartung, H.; Kluge, R.; Ströhl, D.; Fanghänel, E. *Eur. J. Org. Chem.* **2003**, 47−53.

(5) (a) For a review, see: Heathcock, C. H.; Graham, S. L.; Pirrung, M. C.; Plavac, F.; White, C. T. In *The Total Synthesis of Natural Products*; Apsimon, J., Ed.; Wiley-Interscience: New York, 1983; Vol. 5, pp 264−313. (b) Shirafuji, H.; Tsubotani, S.; Ishimaru, T.; Harada, S. Int. Patent PCT, WO91/13887, 1991; *Chem. Abstr.* **1991**, *116*, 39780. (c) Sakamoto, K.; Tsuji, E.; Abe, F.; Nakanishi, T.; Yamashita, M.; Shigematsu, N.; Izumi, S.; Okuhara, M. *J. Antibiot.* **1996**, *49*, 37−44. (d) Biard, J. F.; Guyot, S.; Roussakis, C.; Verbist, J. F.; Vercauteren, J.; Weber, J. F.; Boukef, K. *Tetrahedron Lett.* **1994**, *35*, 2691−2694. (e) Blackman, A. J.; Li, C.; Hockless, D. C. R.; Skelton, B. W.; White, A. H. *Tetrahedron* **1993**, *49*, 8645−8656.

(6) For some other methods for the preparation of spirodienones involving anisoles or phenols with tethered electrophiles, see: (a) Baird, R.; Winstein, S. *J. Am. Chem. Soc.* **1962**, *84*, 788−792. (b) Wata, C.; Nakamura, S.; Shinoo, Y.; Fusaka, T.; Okada, H.; Kishimoto, M.; Uetsuji, H.; Maezaki, N.; Yamada, M.; Tanaka, T. *Chem. Pharm. Bull.* **1985**, *33*, 1961−1968. (c) Marx, J. N.; Bih, Q. R. *J. Org. Chem.* **1987**, *52*, 336−338. (d) Kende, A. S.; Koch, K. *Tetrahedron Lett.* **1986**, *27*, 6051−6054. (e) Iwata, C.; Yamada, M.; Fusaka, T.; Miyashita, K.; Nakamura, A.; Tanaka, T.; Fujiwara, T.; Tomita, K. *Chem. Pharm. Bull.* **1987**, *35*, 544−552.

(7) The substitution of a silyl group in a vinylsilane by ICl has been reported. See: Funk, R. L.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1980**, *102*, 5245−5253.

(8) Larock, R. C.; Doty, M. J.; Tian, Q.; Zenner, J. M. *J. Org. Chem.* **1997**, *62*, 7536−7537.

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