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Electrophilic *ipso*-Iodocyclization of *N*-(4-Methylphenyl)propiolamides: Selective Synthesis of 8-Methyleneazaspiro[4,5]trienes

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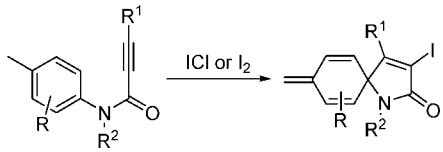
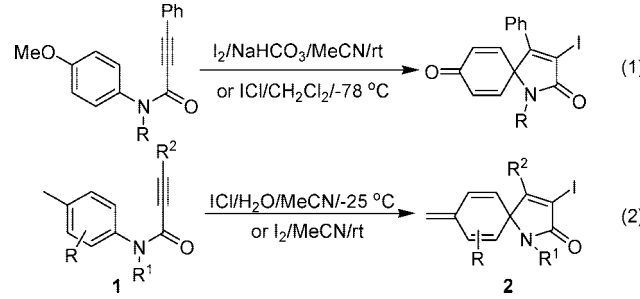


A novel and selective method for the synthesis of 8-methylenespiro[4,5]trienes via intramolecular electrophilic *ipso*-iodocyclization of *N*-(4-methylphenyl)propiolamides has been developed. In the presence of ICl or I_2, 8-methylene-1-azaspiro[4,5]trienes were selectively prepared from the electrophilic *ipso*-iodocyclization of *N*-(4-methylphenyl)propiolamides in moderate to good yields.

The spiro[4,5]decane compounds are valuably synthetic intermediates as well as prevalently structural units in many naturally occurring and biologically active compounds.[1] The majority of methods for the selective synthesis of spiro[4,5]decanes include the oxidative *ipso*-cyclization reactions of the corresponding aryl nitrenium ions bearing an active *para*-group, such as methoxy, hydroxyl, dimethylamino, or halo groups, by hypervalent iodides.[2–5] Kikugawa and co-workers, for example, have reported that in the presence of hypervalent iodides a variety of aryl nitrenium ions bearing methoxy, fluoro, chloro, and bromo at the 4-position of the aromatic ring, such as

SCHEME 1



N-methoxy-(4-substituted aryl)amides[2a] or *N*-phthalimido-3,4-(4-halophenyl)propanamides,[2b] underwent the intramolecular oxidative *ipso*-cyclization reactions to selectively give 1-azaspiro[4,5]decanes in moderate to good yields. Recently, the Fanghänel group[3a] and the Larock group[3b] independently developed another novel route to synthesize the spiro[4,5]trienones by the intramolecular electrophilic *ipso*-cyclization of 4-(4-methoxyaryl)-1-alkynes using ICl or I_2/$NaHCO_3$ system (eq 1 in Scheme 1). To the best of our knowledge, a methyl group as an active *para*-group for the *ipso*-cyclization reaction still remains an unexplored area. Here, we wish to report that 4-(*p*-methylaryl)-1-alkynes could undergo the intramolecular *ipso*-iodocyclization process with ICl or I_2 to afford the corresponding 8-methylene-1-azaspiro[4,5]trienes in moderate to good yields (eq 2).[4]

The reactions of *N*-methyl-3-phenyl-*N*-*p*-tolylpropiolamide (**1a**) with iodine reagents were conducted to screen the optimal reaction conditions, and the results are summarized in Table 1. No reaction was observed when amide **1a** was treated with ICl in MeCN at −78 °C (entry 1). To our delight, the target product

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(1) 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, 264−313. (b) Yoneda, K.; Yamagata, E.; Nakanishi, T.; Nagashima, T.; Kawasaki, I.; Yoshida, T.; Mori, H.; Miura, I. *Phytochemistry* **1984**, *23*, 2068–2069. (c) Sakamoto, K.; Tsujii, 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. (f) Du, Y.; Lu, X. *J. Org. Chem.* **2003**, *68*, 6463–6465. (g) Amagata, T.; Minoura, K.; Numata, A. *J. Nat. Prod.* **2006**, *69*, 1384–1388. (h) Galliford, C. V.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 8748–8758.

(2) For selected papers on the synthesis of the spiro[4,5]decane skeleton by the intramolecular oxidative *ipso*-cyclization reactions of nitrenium ions, see: (a) Kawashima, T.; Naganuma, K.; Okazaki, R. *Organometallics* **1998**, *17*, 376–372. (b) Wardrop, D. J.; Basak, A. *Org. Lett.* **2001**, *3*, 1053–1056. (c) Miyazawa, E.; Sakamoto, T.; Kikugawa, Y. *J. Org. Chem.* **2003**, *68*, 5429–5432. (d) Kikugawa, Y.; Nagashima, A.; Sakamoto, T.; Miyazawa, E.; Shiiya, M. *J. Org. Chem.* **2003**, *68*, 6739–6744. (e) Wardrop, D. J.; Landrie, C. L.; Ortíz, J. A. *Synlett* **2003**, 1352–1354. (f) Wardrop, D. J.; Burge, M. S. *J. Org. Chem.* **2005**, *70*, 10271–10284. (g) Dohi, T.; Maruyama, A.; Minamitsuji, Y.; Takenaga, N.; Kita, Y. *Chem. Commun.* **2007**, 1224–1226.

(3) (a) Appel, T. R.; Yehia, N. A. M.; Baumeister, U.; Hartung, H.; Kluge, R.; Ströhl, D.; Fanghänel, E. *Eur. J. Org. Chem.* **2003**, 47–53. (b) Zhang, X.; Larock, R. C. *J. Am. Chem. Soc.* **2005**, *127*, 12230–12231.

(4) We have also developed a general and selective protocol for the synthesis of spiro[4,5]trienyl acetates via an intramolecular electrophilic *ipso*-cyclization of *N*-arylpropiolamides with NIS and HOAc, in which no active substitutes at the *para*-position of the *N*-aryl ring were required; see: Tang, B.-X.; Tang, D.-J.; Tang, S.; Yu, Q.-F.; Zhang, Y.-H.; Liang, Y.; Zhong, P. *Org. Lett.* **2008**, *10*, 1063–1066.

(5) For selected papers on the synthesis of the spiro[4,5]decane skeleton by the other *ipso*-cyclization methods, see: (a) Kende, A. S.; Koch, K. *Tetrahedron Lett.* **1986**, *27*, 6051–6054. (b) Haack, R. A.; Beck, K. R. *Tetrahedron Lett.* **1989**, *30*, 1605–1608. (c) Nagao, Y.; Lee, W. S.; Jeong, I.-Y.; Shiro, M. *Tetrahedron Lett.* **1995**, *36*, 2799–2802. (d) Boyle, F. T.; Hares, O.; Matusiak, Z. S.; Li, W.; Whiting, D. A. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2707–2711. (e) Blay, G.; Cardona, L.; Collado, A. M.; García, B.; Morcillo, V.; Pedro, J. R. *J. Org. Chem.* **2004**, *69*, 7294–7302. (f) Pearson, A. J.; Wang, X.; Dorange, I. B. *Org. Lett.* **2004**, *6*, 2535–2538. (g) Pigge, F. C.; Coniglio, J. J.; Rath, N. P. *Organometallics* **2005**, *24*, 5424–5430. (h) Pigge, F. C.; Coniglio, J. J.; Dalvi, R. *J. Am. Chem. Soc.* **2006**, *128*, 3498–3499. (i) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2002**, *102*, 2523–2584. (j) Wang, Z.; Xi, Z. *Synlett* **2006**, 1275–1277. (k) Liu, L.; Wang, Z.; Zhao, F.; Xi, Z. *J. Org. Chem.* **2007**, *72*, 3484–3491.

10.1021/jo800328a CCC: $40.75
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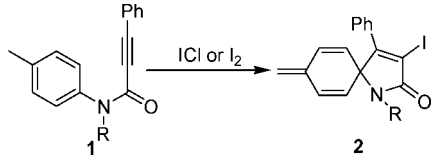
TABLE 1. Screening Optimal Conditions[a]



entry	R	[I]	H_2O (mL)	t (°C)	time (h)	yield (%)[b]
1	Me (**1a**)	ICl	—	−78	1	0 (**2a**)
2	Me (**1a**)	ICl	—	−25 to rt	1	63 (**2a**)
3	Me (**1a**)	ICl	H_2O (0.1)	−25 to rt	1	81 (**2a**)
4	Me (**1a**)	ICl	H_2O (0.3)	−25 to rt	1	33 (**2a**)
5	Me (**1a**)	I_2	—	rt	24	88 (**2a**)
6	Me (**1a**)	I_2	H_2O (0.1)	rt	24	89 (**2a**)
7[c]	Me (**1a**)	I_2	—	rt	24	48 (**2a**)
8	Me (**1a**)	NIS	—	rt	24	0 (**2a**)
9	Me (**1a**)	NaIO	H_2O (0.1)	rt	24	trace (**2a**)
10	H (**1b**)	ICl	H_2O (0.1)	−25 to rt	1	NR (**2b**)
11	H (**1b**)	I_2	—	rt	24	trace (**2b**)
12	Ac (**1c**)	ICl	H_2O (0.1)	−25 to rt	1	NR (**2c**)
13	Ac (**1c**)	I_2	—	rt	24	trace (**2c**)
14	Bn (**1d**)	ICl	H_2O (0.1)	−25 to rt	1	NR (**2d**)
15	Bn (**1d**)	I_2	—	rt	24	48 (**2d**)

[a] Reaction conditions: **1** (0.3 mmol), ICl (1.5 equiv) or I_2 (2 equiv), H_2O and MeCN (3 mL). NR = no reaction. [b] Isolated yield. [c] $NaHCO_3$ (2 equiv) was added.

2a could be isolated in a 63% yield from the reaction of amide **1a** with ICl at −25 °C for 0.5 h and then heating to room temperature for another 0.5 h (entry 2). We found that the amount of water affected the reaction to some extent. The yield of **2a** was enhanced to 81% in the presence of 0.1 mL of water, whereas 0.2 mL of water provided only a 33% yield (entries 3 and 4). The results demonstrated that I_2 was highly efficient for the reaction with amide **1a** to afford the desired product **2a** in an 88% yield at room temperature (entry 5), and identical results were observed in the presence of 0.1 mL of H_2O (entry 6). However, the yield of **2a** was reduced to 48% in the presence of $NaHCO_3$ (entry 7; Larock's conditions). No reaction was observed at room temperature using NIS or NaIO as the iodine source (entries 8 and 9).[4] It was found that analogous amides with the methyl group replaced by a hydrogen or an acyl group were not suitable substrates for the reaction in the presence of either I_2 or ICl (entries 10−13). Identical results were observed from the reaction of *N*-benzyl-3-phenyl-*N*-*p*-tolylpropiolamide (**1d**) with ICl (entry 14). Gratifyingly, a 48% yield of the target product **2d** was isolated when amide **1d** was treated with I_2 (entry 15).

As listed in Table 2, a variety of *N*-methyl-*p*-tolylpropiolamides **1e**−**s** were evaluated to explore the scope of the electrophilic *ipso*-cyclization reaction under the standard conditions. The results demonstrated that both the electronic effect and the steric effect affected the reaction to some extent. Initially, substitutes on the aromatic ring of the *N*-*p*-tolyl group were tested. We found that a series of functional substitutes, such as methyl, chloro, or bromo groups, were tolerated well. *N*-(2-Bromo-4-methylphenyl)-*N*-methyl-3-phenylpropiolamide (**1g**), for instance, underwent the reaction with I_2 smoothly, providing a 91% yield (entry 4). Amide **1h**, a bulky substrate, was also reacted with ICl to afford the corresponding product **1h** in quantitative yield, but with I_2 gave only 40% yield (entries 5 and 6). Subsequently, substitutes at the terminal of the C≡C bond of *N*-methyl-*p*-tolylpropiolamides were evaluated. The results showed that terminal alkynes **1i** and **1n** were not suitable for the reaction under the standard conditions. Substrate **1i** treated with I_2 afforded only 11% yield of the target product **2i**, and with ICl did not work (entries 7 and 8). Similar results were obtained using terminal alkyne **1n** as the substrate (entries 13 and 14). To our delight, substrates bearing a methyl, electron-withdrawing aryl, or electron-neutral aryl group at the terminal of the C≡C bond of propiolamide all worked well with ICl or I_2 in moderate to good yields (entries 15−19). Unfortunately, attempts at the electrophilic *ipso*-cyclization of amide **1s**, having an electron-donating aryl group at the terminal of propiolamide, with either ICl or I_2 failed (entries 20 and 21). The electrophilic *ipso*-cyclization of *N*-(4-butylphenyl)-*N*-methyl-3-phenylpropiolamide (**1t**) with ICl also proceeded successfully in a 65% yield, but the reaction of **1t** with I_2 provided a low yield (entries 22 and 23).

Other substrates, including amides **1u**−**v**, amine **1w**, and ester **1x**, were further explored under the standard conditions, and the results are summarized in Scheme 2. The results revealed that 4-(*p*-methoxyaryl)-1-alkyne **1u** was a suitable substrate to undergo the electrophilic *ipso*-cyclization reaction with ICl or I_2 to give *N*-methyl-3-iodo-4-phenyl-1-azaspiro[4,5]-deca-3,6,9-trien-8-one (**2u**) in good yields, which is similar to those of Larock's results (eq 3 in Scheme 2).[3a] However, *N*-methyl-3-phenyl-*N*-*o*-tolylpropiolamide (**1v**) reacted with either ICl or I_2 and afforded an *ortho*-cyclized product **3v**, not the target *ipso*-cyclized product (eq 4 in Scheme 2). Unfortunately, both amine **1w** and ester **1x** were found to be unsuitable substrates for the reaction under the standard conditions (eqs 5 and 6 in in Scheme 2).[6]

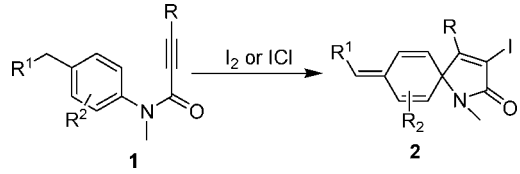
A working mechanism as outlined in Scheme 3 for the electrophilic *ipso*-cyclization reaction is proposed on the basis of the present results and the previously reported mechanisms.[2,3,7] The iodonium intermediate **A** is readily generated by the interaction of the electrophilic iodine reagent (ICl or I_2) with the alkyne moiety followed by the intramolecular *ipso*-electrophilic cyclization reaction of intermediate **A** to form intermediate **B**.[2,3,6] Among the possible transition states of intermediate **B**, intermediate **C** is the most stable transition state. Finally, intermediate **C** undergoes the β-H elimination process to yield the corresponding product **2**.

In summary, we have developed a novel intramolecular electrophilic *ipso*-cyclization reaction method for the synthesis of 8-methyleneazaspiro[4,5]trienes. In the presence of ICl or I_2, a variety of *N*-(4-methylphenyl)propiolamides successfully

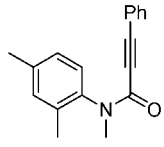
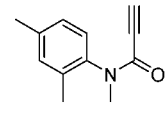
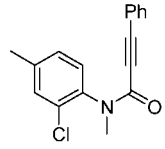
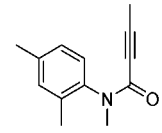
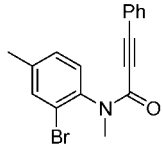
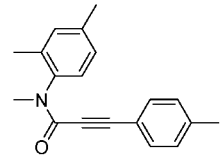
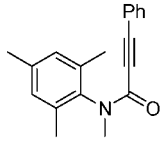
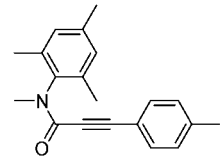
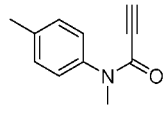
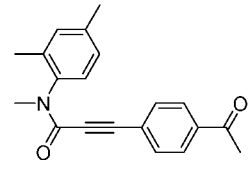
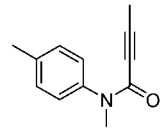
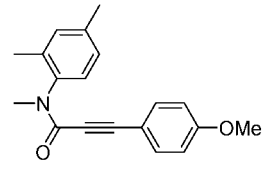
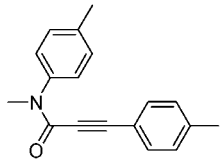
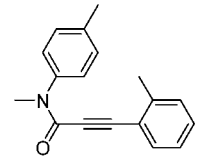
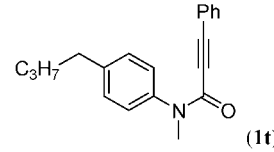
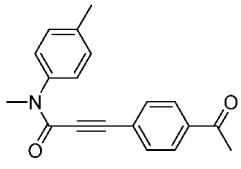
(6) For selected recent papers on the electrophilic iodocyclizations of alkynes, see: (a) Zhang, X.; Campo, M. A.; Yao, T.; Larock, R. C. *Org. Lett.* **2005**, *7*, 763–766. (b) Yao, T.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 1432–1437. (c) Yao, T.; Campo, M. A.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 3511–3517. (d) Yue, D.; Yao, T.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 10292–10296. (e) Yue, D.; Yao, T.; Larock, R. C. *J. Org. Chem.* **2006**, *71*, 62–69. (f) Hu, T.; Liu, K.; Shen, M.; Yuan, X.; Tang, Y.; Li, C. *J. Org. Chem.* **2007**, *72*, 8555–8558. (g) Pattarozzi, M.; Zonta, C.; Broxterman, Q. B.; Kaptein, B.; De Zorzi, R.; Randaccio, L.; Scrimin, P.; Licini, G. *Org. Lett.* **2007**, *9*, 2365–2368. (h) Worlikar, S. A.; Kesharwani, T.; Yao, T.; Larock, R. C. *J. Org. Chem.* **2007**, *72*, 1347–1353. (i) Ciochina, R.; Grossman, R. B. *Chem. Rev.* **2006**, *106*, 3963–3986. (j) Bi, H.-P.; Guo, L.-N.; Duan, X.-H.; Gou, F.-R.; Huang, S.-H.; Liu, X.-Y.; Liang, Y.-M. *Org. Lett.* **2007**, *9*, 397–400. (k) Fischer, D.; Tomeba, H.; Pahadi, N. K.; Patil, N. T.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 4764–4766. (l) Barluenga, J.; Vazquez-Villa, H.; Ballesteros, A.; Gonzalez, J. M. *J. Am. Chem. Soc.* **2003**, *125*, 9028–9029. (m) Barluenga, J.; Vazquez-Villa, H.; Ballesteros, A.; Gonzalez, J. M. *Org. Lett.* **2003**, *5*, 4121–4123. (n) Barluenga, J.; Trincado, M.; Rubio, E.; Gonzalez, J. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 2406–2409. (o) Barluenga, J.; Trincado, M.; Rubio, E.; Gonzalez, J. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 3140–3143. (p) Barluenga, J.; Palomas, D.; Rubio, E.; Gonzalez, J. M. *Org. Lett.* **2007**, *9*, 2823–2826.

(7) The two reactions of amine **1w** and ester **1x** were determined by GC-MS analysis. The results showed that no products were observed from the reaction of **1w**, but 1,2-diiodoalkene (*p*-tolyl 2,3-diiodo-3-phenylacrylate) was detected from the reaction of **1x**. Thus, we deduced that the electronic effect of the substrates plays a crucial role in the reaction.

TABLE 2. Electrophilic *ipso*-Iodocyclization of *N*-Arypropiolamides (1)[a,b]

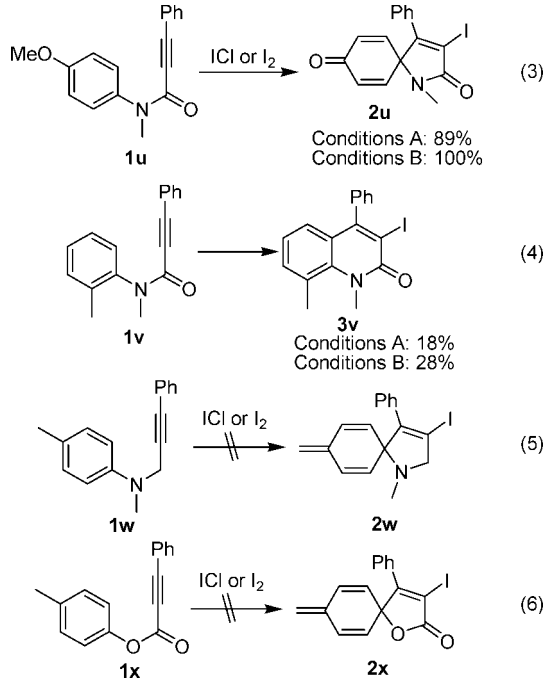


1 2

Entry	Substrate	[I][a]	Yield (%)[b]	Entry	Substrate	[I][a]	Yield (%)[b]
1	 (**1e**)	ICl	77 (**2e**)	13	 (**1n**)	ICl	trace (**2n**)
2	(**1e**)	I_2	76 (**2e**)	14	(**1n**)	I_2	messy (**2n**)
3	 (**1f**)	I_2	85 (**2f**)	15	 (**1o**)	I_2	55 (**2o**)
4	 (**1g**)	I_2	91 (**2g**)	16	 (**1p**)	ICl	89 (**2p**)
5	 (**1h**)	ICl	100 (**2h**)	17	(**1p**)	I_2	40 (**2p**)
6	(**1h**)	I_2	40 (**2h**)	18	 (**1q**)	ICl	80 (**2q**)
7	 (**1i**)	ICl	NR (**2i**)	19	 (**1r**)	I_2	91 (**2r**)
8	(**1i**)	I_2	8 (**2i**)				
9	 (**1j**)	I_2	40 (**2j**)	20	 (**1s**)	ICl	trace (**2s**)
10	 (**1k**)	I_2	66 (**2k**)	21	(**1s**)	I_2	trace (**2s**)
11	 (**1l**)	I_2	70 (**2l**)	22	 (**1t**)	ICl	65 (**2t**)
12	 (**1m**)	I_2	69 (**2m**)	23	(**1t**)	I_2	13 (**2t**)

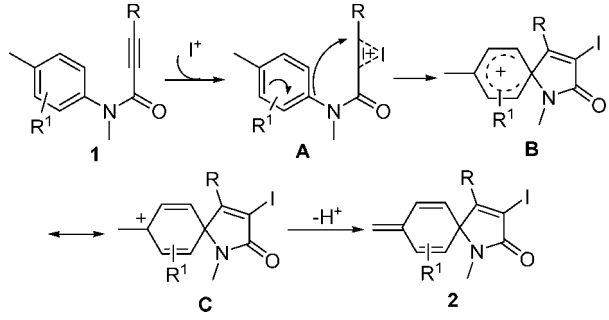
[a] Conditions A: **1** (0.3 mmol), MeCN (3 mL), ICl (1.5 equiv), and H_2O (0.1 mL) at −25 °C (0.5 h) to room temperature (0.5 h). Conditions B: **1** (0.3 mmol), MeCN (3 mL), and I_2 (2 equiv) at room temperature for 24 h. NR = no reaction. [b] Isolated yield.

SCHEME 2. The *ipso*-Cyclization of Other Substrates[a]



[a] Conditions A: **1** (0.3 mmol), MeCN (3 mL), ICl (1.5 equiv), and H_2O (0.1 mL) at −25 °C (0.5 h) to room temperature (0.5 h). Conditions B: **1** (0.3 mmol), MeCN (3 mL), and I_2 (2 equiv) at room temperature for 24 h.

SCHEME 3. A Working Mechanism



underwent the electrophilic *ipso*-iodocyclization reaction to selectively prepare 4-methyleneazaspiro[4,5]trienes in moderate to excellent yields. Moreover, both an iodo and a methylene group on these products provides an attractive and useful route to introduce new groups for the synthesis of new bioactive products. Efforts to study the detailed mechanism and extend the application of the *ipso*-cyclization transformations in organic synthesis are underway in our laboratory.

Experimental Section

Typical Experimental Procedure for the *ipso*-Electrophilic Cyclization of *N*-(4-Methylpheny)propiolamides with ICl: A mixture of *N*-(4-methylaryl)propiolamides **1** (0.3 mmol), ICl (1.5 equiv), and H_2O (0.1 mL) in MeCN (3 mL) was stirred at −25 °C (0.5 h) to room temperature (0.5 h) until complete consumption of starting material as monitored by TLC and GC analysis. Then the mixture was washed with saturated NaS_2O_3 and extracted with diethyl ether. The organic layers were dried with Na_2SO_3 and evaporated under vacuum, and the residue was purified by flash column chromatography to afford the pure product (hexane/ethyl acetate).

Typical Experimental Procedure for the *ipso*-Electrophilic Cyclization of *N*-(4-Methylphenyl)propiolamides with I_2: A mixture of *N*-(4-methylaryl)propiolamides **1** (0.3 mmol) and I_2 (2 equiv) in MeCN (3 mL) and/or H_2O (0.1 mL) was stirred at room temperature for 24 h until complete consumption of starting material as monitored by TLC and GC analysis. Then the mixture was washed with saturated NaS_2O_3 and extracted with diethyl ether. The organic layers were dried with Na_2SO_3 and evaporated under vacuum, and the residue was purified by flash column chromatography to afford the pure product (hexane/ethyl acetate).

***N*-Methyl 3-Iodo-4-phenyl-8-methylenespiro[4,5]triene (2a):** Pale yellow solid, mp 177.6−178.8 °C (uncorrected); ^{1}H NMR (400 MHz) δ 7.47 (d, J = 8.0 Hz, 2H), 7.36 (d, J = 6.8 Hz, 3H), 6.58 (d, J = 9.6 Hz, 2H), 5.44 (d, J = 9.6 Hz, 2H), 5.20 (s, 2H), 2.87 (s, 3H); ^{13}C NMR (100 MHz) δ 167.0, 162.2, 134.9, 133.3, 132.2, 129.4, 128.3, 128.0, 126.1, 119.7, 96.0, 70.9, 26.4; IR (KBr, cm^{-1}) 1699, 1637, 1588; LRMS (EI, 70 eV) *m*/*z* (%) 375 (M^+, 10), 248 (88), 129 (100); HRMS (EI) for $C_{17}H_{14}INO$ (M^+) calcd 375.0120, found 375.0120.

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Supporting Information Available: General experimental procedures, compounds **2** and **3v** characterization data, and copies of spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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