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Selective Synthesis of Spiro[4,5]trienyl Acetates via an Intramolecular Electrophilic *ipso*-Iodocyclization Process

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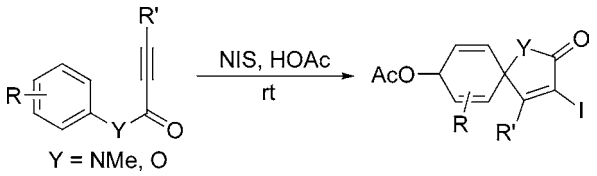
ABSTRACT



A general and efficient intramolecular electrophilic *ipso*-iodocyclization of para-unactivated arylalkynes has been developed for the synthesis of spiro[4,5]trienyl acetates. In the presence of NIS (*N*-iodosuccimide) and HOAc, para-unactivated arylalkynes, including *N*-arylpropiolamides and phenyl 3-phenylpropiolate, underwent the intramolecular electrophilic *ipso*-iodocyclization smoothly in moderate to good yields.

Electrophilic cylizations of arylalkynes have emerged as an important topic in organic chemistry because their products, heterocycles and carbocycles, have found widespread use in the synthesis of natural and biologically active products.[1,2] Currently, the vast majority of these electrophilic cyclization methods are worked between alkyne and *o*-arene substitutions to construct heterocycles and carbocycles.[1] Recent work has provided another novel route to these compounds by electrophilic *ipso*-cyclization of arylalkynes (eq 1).[2] In the presence of halogen electrophiles, 4-(para-substituted aryl)-1-alkynes underwent the electrophilic *ipso*-halocyclization reaction smoothly to give azaspiro[4,5]trienones in good yields. Unfortunately, the *ipso*-cyclization method is limited to aryl compounds bearing some para substituents, such as methoxy and *N*,*N*-dimethylamino groups, on the aryl rings. Thus, alternative methods for the electrophilic *ipso*-cyclization of para-unactivated arylalkynes remain a challenging task. After a series of trials, we were happy to find that

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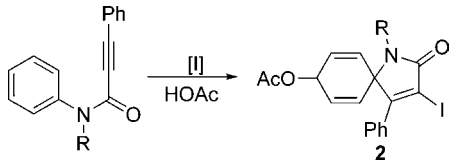
N-arylpropiolamides and phenyl 3-phenylpropiolate could undergo the intramolecular electrophilic *ipso*-iodocyclization/nucleophilic addition process with NIS (*N*-iodosuccimide) and HOAc to selectively afford spiro[4,5]trienyl acetates in moderate to good yields (eq 2).[3,4] This work now presents the first examples for extending the electrophilic *ipso*-cyclization of *p*-methoxyarylalkynes to para-unactivated arylalkynes.

N-Methyl-*N*,3-diphenylpropiolamide (**1a**) was chosen as the starting substrate to screen the optimal reaction conditions, and the results are summarized in Table 1. To our

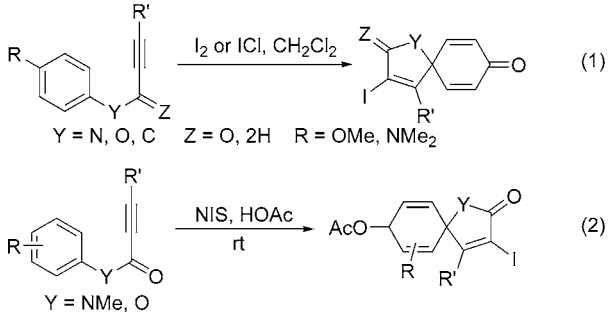
Table 1. Screening Conditions[a]



entry	R	[I] (equiv)	*t* (°C)	time (h)	isolated yield (%) *cis*-**2**	*trans*-**3**
1	Me (**1a**)	NIS (1.5)	25	3	43	35
2	Me (**1a**)	ICl (1.5)	25	3	38	13
3	Me (**1a**)	I_2 (2.0)	25	3	trace	trace
4	Me (**1a**)	NIS (1.5)	60	0.6	42	18
5	H (**1b**)	NIS (1.5)	25	3	0	0
6	acetyl (**1c**)	NIS (1.5)	25	3	0	0
7	allyl (**1d**)	NIS (1.5)	25	3	0	0
8[b]	Me (**1a**)	NBS (1.5)	25	3	0	0

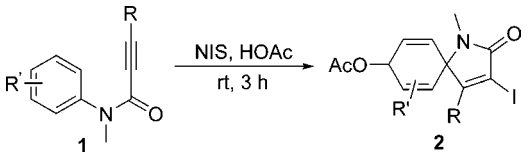
[a] Reaction conditions: **1** (0.4 mmol) and HOAc (1 mL). [b] No bromocyclization reaction was observed.

delight, the reaction of amide **1a** with NIS in HOAc proceeded selectively to afford the corresponding *cis*- and *trans*-3-iodoazaspiro[4,5]trienyl acetates **2a** in 43% and 35% yields, respectively (entry 1).[5] The yields of both *cis*- **2a** and *trans*-**2a** were reduced to some extent using ICl instead of NIS (entry 2). However, no desired *ipso*-cyclization products were isolated in the presence of I_2 (entry 3). Subsequently, the temperature effect was investigated, and it turned out that room temperature gave the better results (entries 1 and 4). Although the reaction rate was enhanced at 60 °C, the total yield was decreased. It is noteworthy that no reaction is observed from the analogous amides with the methyl group replaced by a hydrogen, acetyl, or allyl group (entries 5−7). Finally, attempts at *ipso*-bromocyclization reaction of amide **1a** with NBS failed (entry 8).



These results prompted us to explore the scope of the intramolecular *ipso*-iodocyclization reaction under the optimal conditions (Table 2). As shown in Table 2, a variety

Table 2. Intramolecular Electrophilic *ipso*-Iodocyclizations of **1** with NIS and HOAc[a]



entry	R/R′	isolated yield (%) *cis*-**2**	*trans*-**2**
1	C_6H_5/2-Me (**1e**)	50	38
2	C_6H_5/3-Me (**1f**)	34	39
3	C_6H_5/2,5-diMe (**1 g**)	53	33
4	C_6H_5/2,3-diMe (**1h**)	48	30
5	C_6H_5/2-Cl (**1i**)	48	50
6	C_6H_5/2-Br (**1j**)	43	44
7	C_6H_5/2-I (**1k**)	44	44
8	C_6H_5/2-CH_3CO (**1l**)	trace	trace
9	4-MeC_6H_4/H (**1 m**)	39	35
10	4-MeOC_6H_4/H (**1n**)	47	18
11	4-MeCOC_6H_4/H (**1o**)	trace	trace
12	Me/H (**1p**)	17	45
13	H/H (**1q**)	trace	trace

[a] Reaction conditions: **1** (0.4 mmol), NIS (0.6 mmol), and HOAc (1 mL) at room temperature for 3 h.

of amides **1e**−**q** were examined in the presence of NIS and HOAc. The results demonstrated that several functional groups, such as methyl, chloro, bromo, iodo, and methoxy groups, on the aromatic ring of amides were tolerated well under the standard conditions. First, a number of *N*-aryl

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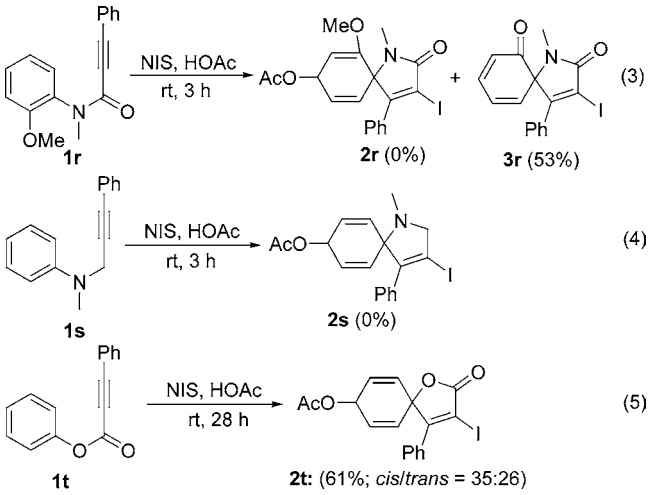
(4) For selected papers on the synthesis of the spiro[4,5]decane skeleton by the other methods, see: (a) Kende, A. S.; Koch, K. *Tetrahedron Lett.* **1986**, *27*, 6051−6054. (b) Haack, R. A.; Beck, K. R. *Tetrahedron Lett.* **1989**, *30*, 1605−1608. (c) Nagao, Y.; Lee, W. S.; Jeong, I.-Y.; Shiro, M. *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.

groups of the amides **1f**−**l** were examined. We found that *N*-methyl-*N*-aryl-3-phenylpropiolamides **1f**−**k**, having electron-donated groups on the N-aromatic ring, all work well with NIS and HOAc, but amide **1l** bearing an electron-withdrawing group failed to generate the target *ipso*-iodocyclization products. *N*-(2-Iodophenyl)-*N*-methyl-3-phenylpropiolamide (**1k**), for instance, underwent the intramolecular *ipso*-iodocyclization reaction with NIS and HOAc smoothly to provide the *cis*- and *trans*-azaspiro[4,5]trienyl acetates **2k** in 44% and 44% yields, respectively (entry 7). However, substrate **1l** bearing a 2-acetyl group was not a suitable substrate for the reaction. Subsequently, amides bearing some substitutes at the terminal of alkyne were then investigated. We found that amides **1m-n** and **1p** having the 4-methylphenyl, 4-methoxyphenyl or methyl group at the terminal of alkyne, were treated with NIS and HOAc smoothly in moderate to good yields (entries 9, 10, and 12), whereas the reactions of substrates **1o** and **1q**, bearing an 4-acetylphenyl or a hydrogen group, was unsuccessful (entries 11 and 13).

As listed in Scheme 1, we were surprised to find that amide **1r**, bearing an *o*-methoxy group on the *N*-aryl ring, could also undergo the *ipso*-iodocyclization reaction with NIS in

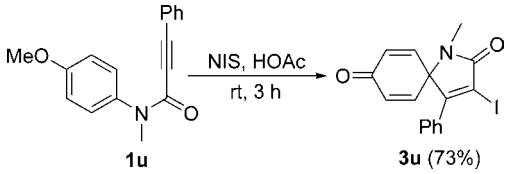
Scheme 1. *ipso*-Iodocyclization Reaction



HOAc smoothly to give *N*-methyl-3-phenyl-1-azaspiro[4,5]-deca-3,6,8-trien-10-one (**3r**), not the target azaspiro[4,5]-trienyl acetate **2r**, in a 53% yield (eq 3). Subsequently, an amine **1s** and an ester **1t** were also examined under the standard conditions. Unfortunately, *N*-methyl-*N*-(3-phenyl-prop-2-ynyl)benzenamine (**1s**) was observed to be an unsuitable substrate for the *ipso*-iodocyclization reaction under the same conditions (eq 4). Note that the reaction of phenyl 3-phenylpropiolate (**1t**) with NIS and HOAc proceeds smoothly to afford the desired oxaspiro[4,5]trienyl acetate **2t** in a good total yield (eq 5).

To elucidate the mechanism, a controlled reaction was conducted under the standard conditions (Scheme 2). In the

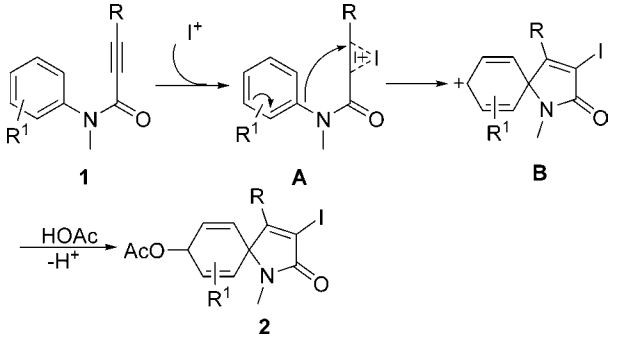
Scheme 2. Two Controlled Reactions



presence of NIS and HOAc, a product identical to that in previous papers[2b] was observed from the reaction of *N*-(4-methoxyphenyl)-*N*-methyl-3-phenylpropiolamide (**1u**) with NIS in HOAc.

A working mechanism as outlined in Scheme 3 was proposed on the basis of the present results and the previously

Scheme 3. Working Mechanism



reported mechanisms.[1−3] Initially, the iodonium intermediate **A** is generated by the interaction of the electrophilic NIS with the alkyne moiety followed by the intramolecular electrophilic *ipso*-cyclization of intermediate **A** to form intermediate **B**.[1,2] Finally, attack of intermediate **B** by the nucleophilic HOAc occurs to afford both cis and trans products **2**.

In summary, we have developed a general and efficient protocol for the intramolecular electrophilic *ipso*-cyclization of para-unactivated arylalkynes. In the presence of NIS and HOAc, *N*-arylpropiolamides and phenyl 3-phenylpropiolate underwent the electrophilic *ipso*-cyclization reaction with NIS followed by attack with HOAc to synthesize spiro[4,5]-trienyl acetates in moderate to good yields. Importantly, we have developed a novel route to the synthesis of new type spiro[4,5]decane skeleton, and the known spiro[4,5]decane skeleton is a prevalent motif in many naturally occurring and biologically active compounds.[6] Work to apply the reaction in organic synthesis and develop more novel intramolecular electrophilic *ipso*-cyclization processes is currently underway.

(5) Interestingly, cis and trans isomers can be separated by flash column chromatography using hexane/ethyl acetate as the eluent. The structure and the cis and trans configuration of the products **2** were based upon the chemical shift of the 8-proton by comparison with the authoritative data of ref 2d and were unambiguously assigned by X-ray analysis of the product *cis*-**2i**; see the Supporting Information.

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Supporting Information Available: Analytical data and spectra (^{1}H and ^{13}C NMR) for all products **2** and **3**; typical procedure for the intramolecular electrophilic *ipso*-iodocyclization reaction. This material is available free of charge via the Internet at http://pubs.acs.org.

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