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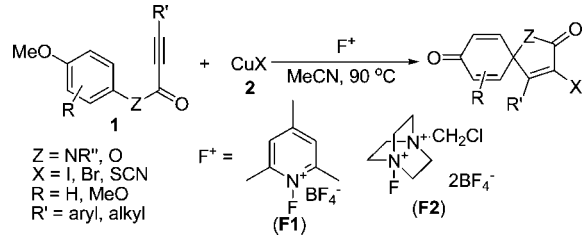
Electrophilic *ipso*-Cyclization of *N*-(*p*-Methoxyaryl)propiolamides Involving an Electrophile-Exchange Process

Bo-Xiao Tang,[†] Qin Yin,[†] Ri-Yuan Tang,[‡] and Jin-Heng Li*,[†,‡]

Key Laboratory of Chemical Biology & Traditional Chinese Medicine Research, Hunan Normal University, Changsha 410081, China, and College of Chemistry and Materials Science, Wenzhou University, Wenzhou 325035, China

jhli@hunnu.edu.cn

Received August 15, 2008



A novel electrophilic *ipso*-cyclization involving an electrophile-exchange process has been developed. In the presence of CuX (X = I, Br, SCN) and electrophilic fluoride reagents, a variety of *N*-(*p*-methoxyaryl)propiolamides and 4-methoxyphenyl 3-phenylpropiolate were cyclized to selectively afford the corresponding spiro[4.5]decenones in moderate to good yields. It is noteworthy that two azaquaternary tricyclic products were synthesized through a two-step pathway involving an electrophilic *ipso*-cyclization and then an intramolecular Heck reaction.

Introduction

Recently, the electrophilic cyclization method has been proven to be a powerful tool for the synthesis of highly functionalized heterocyclic and carbocyclic compounds.[1−3] Generally, the method is worked via two pathways: (1) between a alkyne and an *o*-arene substitute to construct benzo-heterocycle and benzo-carbocycle compounds,[1,2] and (2) between a alkyne and an *ipso*-arene substitute to construct spirocycle compounds.[3] However, only four papers have been reported on the electrophilic cyclization by the latter pathway.[3] Moreover, the electrophiles are limited to halogens, such as ICl, I_2, NIS (*N*-iodosuccimide), and Br_2, in all cases. In the presence of halogen electrophiles, 4-(*p*-substituted aryl)-1-alkynes underwent the electrophilic *ipso*-

[†] Hunan Normal University.
[‡] Wenzhou University.

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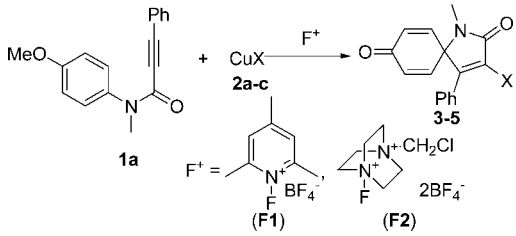
10.1021/jo8018297 CCC: $40.75
Published on Web 10/17/2008

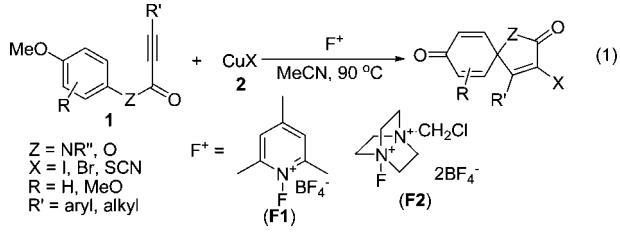
TABLE 1. Screening Optimal Conditions[a]



entry	CuX	*t* (°C)	F^+	yield (%)[b]
1	CuI (**2a**)	r.t	**F1**	trace (**3**)
2	CuI (**2a**)	60	**F1**	60 (**3**)
3	CuI (**2a**)	90	**F1**	87 (**3**)
4	CuI (**2a**)	110	**F1**	76 (**3**)
5	CuI (**2a**)	90	**F2**	74 (**3**)
6	CuI (**2a**)	90	—	0 (**3**)
7[c]	CuI (**2a**)	90	**F1**	70 (**3**)
8[d]	CuI (**2a**)	90	**F1**	69 (**3**)
9	CuBr (**2b**)	90	**F1**	86 (**4**)
10	CuSCN (**2c**)	90	**F1**	13 (**5**)
11	CuSCN (**2c**)	90	**F2**	51 (**5**)

[a] Reaction conditions: **1** (0.2 mmol), CuX (3 equiv), F^+ (1.5 equiv), and MeCN (1 mL). [b] Isolated yield. [c] F^+ (1.0 equiv). [d] CuI (2 equiv).

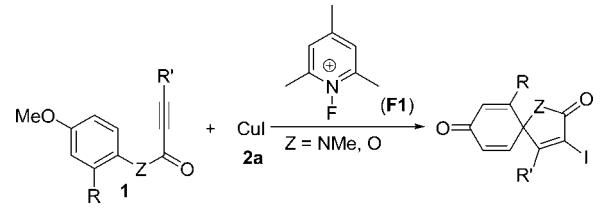
halocyclization reaction smoothly to give the corresponding spiro[4.5]trienes in good yields.[3a−c] Very recently, we have reported that *para*-unsubstituted arylalkynes could also undergo the electrophilic *ipso*-iodocyclization with NIS and HOAc to selectively afford spiro[4.5]trienyl acetates in moderate to good yield.[3d] Importantly, these spirocyclic compounds are pharmacologically important compounds that widely occur in nature products as well as are often utilized as intermediates in organic synthesis.[4] Thus, the development of alternative electrophilic *ipso*-cyclization routes including new electrophiles to the synthesis of spirocyclic compounds is still interesting. Initially, we expected to induce a fluoride onto the spiro[4.5]decene skeleton using electrophilic fluoride reagents, but all the experiments failed. Accidently, we found that the electrophilic *ipso*-cyclization reaction could take place with CuX (CuI, CuBr, and CuSCN) combined with the electrophilic fluoride reagents.[5] Here, we wish to report our detailed results (eq 1).



Results and Discussion

As shown in Table 1, *N*-(4-methoxyphenyl)-*N*-methyl-3-phenylpropiolamide (**1a**) was used as the starting substrate to explore the optimal conditions.[5] We found that the reaction temperature has a fundamental influence on the reaction (entries 1−4). Only a trace amount of the target product **3** was observed from the reaction of amide **1a** with CuI (**2a**) and an electrophilic fluoride reagent **F1**, 1-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate, at room temperature (entry 1), whereas the yield of **3** was enhanced sharply to 60% at 60 °C and the highest yield was obtained at 90 °C (entries 2 and 3). *N*-Fluoro-*N*′-(chloromethyl)triethylenediamine bis(tetrafluoroborate) **F2**, another electrophilic fluoride reagent, was also evaluated, and it was less effective than **F1** (entry 5). Note that no reaction was observed without any electrophilic fluoride reagents (entry 6). Subsequently, the amount of both CuI and **F1** was tested, and it turned out that 3 equiv of CuI and 1.5 equiv of **F1** provided the best results (entries 3, 7, and 8). Finally, a series of salts were also examined by reacting with amide **1a** in the presence of the electrophilic fluoride reagents (entries 9−11).[6] We were happy to observe that both CuBr (**2b**) and CuSCN (**2c**) were highly active for the reaction. It is noteworthy that in the presence of **F1** the reaction of amide **1a** with CuBr (**2b**) provides satisfactory yield (entry 9), but **F2** affords better results than **F1** in the reaction of amide **1a** with CuSCN (**2c**) (entry 11).

TABLE 2. Electrophilic *ipso*-Cyclization of 4-(*p*-Methoxyarylalkynes (1) with CuI (2a) and F1[a]



entry	reagent **1**	Z	R	R′	product	yield (%)[b]
1	**1b**	NH	H	C_6H_5	**6**	16
2	**1c**	NAc	H	C_6H_5	**7**	trace
3	**1d**	NBn	H	C_6H_5	**8**	93
4	**1e**	NMe	H	4-MeC_6H_4	**9**	90
5	**1f**	NMe	H	2-MeC_6H_4	**10**	82
6	**1g**	NMe	H	4-$MeOC_6H_4$	**11**	78
7	**1h**	NMe	H	4-$NO_2C_6H_4$	**12**	45
8	**1i**	NMe	H	4-AcC_6H_4	**13**	48
9	**1j**	NMe	H	Thien-2-yl	**14**	63
10	**1k**	NMe	H	CH_3	**15**	41
11	***1l***	NMe	H	*n*-C_5H_{11}	**16**	32
12	**1m**	NMe	MeO	C_6H_5	**17**	trace
13	**1n**	O	H	C_6H_5	**18**	45

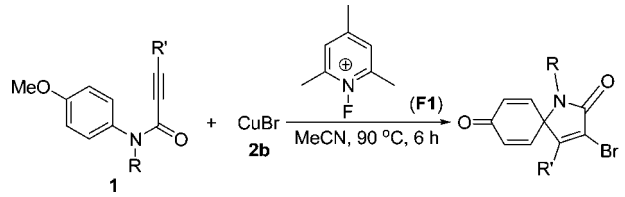
[a] Reaction conditions: **1** (0.2 mmol), CuI (**2a**; 3 equiv), **F1** (1.5 equiv), and MeCN (1 mL) at 90 °C for 6 h. [b] Isolated yield.

With the standard reaction conditions in hand, we then used the CuI/**F1** system to explore the scope of amides (Table 2). The results showed that a variety of amides were suitable substrates to react with CuI (**2a**) and **F1** in moderate to good yields, and the substitutes on the nitrogen, the terminal of C≡C bond, or aromatic ring affected the reaction to some extent. In the presence of CuI (**2a**) and **F1**, amide **1b** bearing a free *N*-H group underwent the electrophilic *ipso*-iodocyclization reaction in 16% yield (entry 1), and the reaction of amide **1c**, having an *N*-acetyl group, was unsuccessful (entry 2). To our delight, substrate **1d** with an *N*-benzyl group afforded the target product (**8**) in good yield (entry 3). Subsequently, the substitutes, either aryl or alkyl, at the terminal C≡C bond were investigated. We found that several functional groups, such as methyl, methoxy, nitro, and acetyl, on the aryl ring were tolerated well, and the yields were reduced to some extent in the presence of the electron-withdrawing group. While amide **1e** bearing a methyl group, for instance, was treated with **2a** and **F1** in 90% yield

(5) For a paper on the X^-/F^+ electrophile-exchange process, see: Syvret, R. G.; Butt, K. M.; Nguyen, T. P.; Bulleck, V. L.; Rieth, R. D. *J. Org. Chem.* **2002**, *67*, 4487.

(6) Other salts, including $CuBr_2$, CuCl, $CuCl_2$, CuCN, KBr, NaCl, and $NaNO_2$, were also examined, and they were less effective. The detailed data are summarized in the Supporting Information.

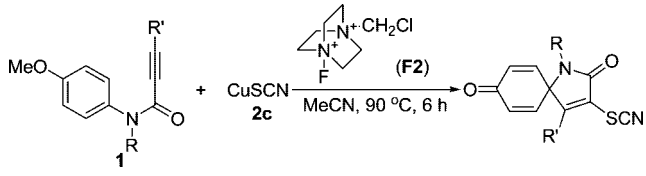
TABLE 3. Electrophilic *ipso*-Cyclization of 4-(*p*-Methoxyarylalkynes (1) with CuBr (2b) and F1[a]



entry	reagent **1**	R	R′	product	yield (%)[b]
1	**1d**	Bn	C_6H_5	**19**	84
2	**1f**	CH_3	2-MeC_6H_4	**20**	71
3	**1g**	CH_3	4-$MeOC_6H_4$	**21**	71

[a] Reaction conditions: **1** (0.2 mmol), CuBr (**2b**; 3 equiv), **F1** (1.5 equiv), and MeCN (1 mL) at 90 °C for 6 h. [b] Isolated yield.

TABLE 4. Electrophilic *ipso*-Cyclization of 4-(*p*-Methoxyarylalkynes (1) with CuBr (2c) and F2[a]



entry	reagent **1**	R	R′	product	yield (%)[b]
1	**1d**	Bn	C_6H_5	**22**	57
2	**1f**	CH_3	2-MeC_6H_4	**23**	43
3	**1g**	CH_3	4-$MeOC_6H_4$	**24**	59

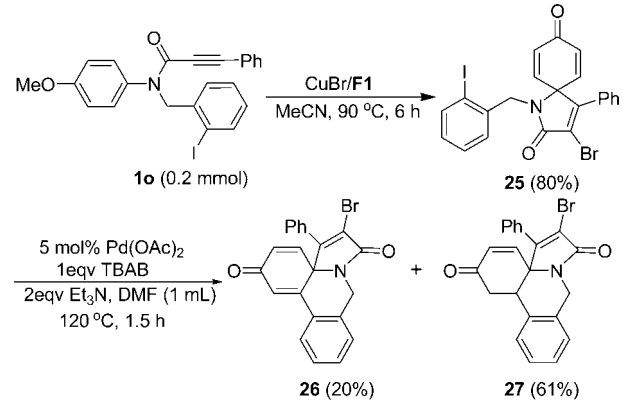
[a] Reaction conditions: **1** (0.2 mmol), CuSCN (**2c**; 3 equiv), **F2** (1.5 equiv), and MeCN (1 mL) at 90 °C for 6 h. [b] Isolated yield.

(entry 4), the yield was decreased to 45% in the reaction of amide **1h** having a nitro group (entry 7). Interestingly, a heterocyclic amide **1j** also underwent reaction with **2a** and **F1** smoothly to afford the corresponding product **14** in 63% yield (entry 9). It was encouraging to discover that alkylalkynes **1k** and **1*l*** were also suitable substrates for the reaction with **2a** and **F1** (entries 10 and 11). Unfortunately, attempts at cyclization of amide **1m** bearing an *o*-methoxy group on the *N*-aryl ring only afforded a trace amount of the target product **17** under the standard reaction conditions (entry 12). It is worth noting that ester **1n** also undergoes the reaction with **2a** and **F1** successfully in 45% yield (entry 13).

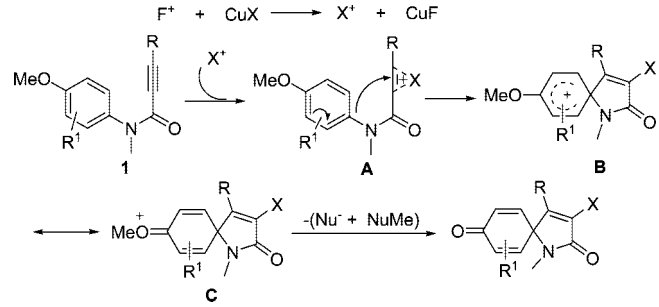
Subsequently, we turned our attention to apply both the CuBr/**F1** system and the CuSCN/**F2** system in the electrophilic *ipso*-cyclization reaction with amides **1** (Tables 3 and 4). As demonstrated in Table 3, the reactions of amides **1d**, **1f**, and **1g** with CuBr (**2b**), respectively, were conducted smoothly in the presence of **F1** to generate the target products in good yields. Substrate **1g** bearing an *o*-methyl group, for instance, underwent the electrophilic *ipso*-bromocyclization reaction with **2a** and **F1** smoothly in 71% yield (entry 2 in Table 3). Next, the reactions of amides **1** with CuSCN (**2c**) and **F2** were also evaluated as listed in Table 4. To our delight, amides **1d**, **1f**, or **1g** were reacted with CuSCN (**2c**) and **F2** successfully to afford the target products in moderate yields (entries 1−3 in Table 4).

The azaquaternary tricyclic skeleton is widely observed in nature products, particularly in alkaloids.[4] Consequently, we decided to construct this kind of alkaloid skeleton (Scheme 1). In the presence of the CuBr/**F1** system, substrate **1o** was cyclized to afford the corresponding product **25** in 80% yield. The product **25** then underwent the intramolecular Heck reaction

SCHEME 1. Synthesis of Azaquaternary Tricyclic Products



SCHEME 2. A Possible Mechanism



with $Pd(OAc)_2$ and TBAB (*n*-tetrabutylammonium bromide) to give two azaquaternary tricyclic products **26** and **27** in good total yield.

A working mechanism as outlined in Scheme 2 was proposed on the basis of the reported mechanism and the present results.[1−3,5] First, a new electrophilic X cation is formed in situ by exchange with an electrophilic fluoride reagent.[5] Subsequently, the electrophilic X cation reacts with the alkyne moiety to afford the onium intermediate **A**, followed by the intramolecular electrophilic *ipso*-cyclization of intermediate **A** to form intermediate **B**, and then intermediate **C**. Finally, attack of intermediate **C** by the nucleophilic reagents occurs to cleave the O−CH_3 bond and generate the target product.

Conclusion

In summary, we describe here the first example of the electrophilic *ipso*-cyclization reaction involving an electrophile-exchange process. In the presence of CuX (X = I, Br, SCN) and electrophilic fluoride reagents, a variety of *N*-(*p*-methoxyaryl)propiolamides and 4-methoxyphenyl 3-phenylpropiolate were cyclized to selectively afford the corresponding spiro[4.5]-decenones in moderate to excellent yields. Noteworthy is that two azaquaternary tricyclic products are synthesized in two steps. Work to probe the detailed mechanism and apply the reaction in organic synthesis is currently underway.

Experimental Section

Typical Experimental Procedure of the Electrophilic *ipso*-Cyclization Reaction. A mixture of amide **1** (0.2 mmol), CuX (X = I, Br, SCN; 3 equiv), and electrophilic fluoride reagent (1.5 equiv) was stirred in CH_3CN (1 mL) at 90 °C for 6 h under nitrogen protection until complete consumption of starting material as monitored by TLC and GC-MS analysis. After the reaction was finished, diethyl ether was poured into the mixture, then filtered

and evaporated under vacuum. The residue was purified by flash column chromatography (hexane/ethyl acetate) to afford the desired product.

***N*-Methyl-3-bromo-4-phenyl-1-azaspiro[4.5]-deca-3,6,9-trien-2,8-dione (4).** White solid, mp 163.5−164.1 °C (uncorrected); ^{1}H NMR (500 MHz) δ 7.43−7.36 (m, 5H), 6.55 (d, J = 10.5 Hz, 2H), 6.50 (d, J = 10.5 Hz, 2H), 2.95 (s, 3H); ^{13}C NMR (125 MHz) δ 183.6, 165.7, 151.2, 144.1, 133.3, 130.1, 130.0, 128.6, 127.7, 119.7, 68.2, 26.6; IR (KBr, cm^{-1}) 1701, 1670; LRMS (EI 70 eV) *m*/z (%) 331 (M^+ + 2, 25), 329 (M^+, 25), 250 (42), 129 (100); HRMS (EI) for $C_{16}H_{12}{}^{79}BrNO_2$ (M^+) calcd 329.0051, found 329.0051.

Typical Experimental Procedure of the Intramolecular Heck Reaction. A mixture of substrate **25** (0.15 mmol), $Pd(OAc)_2$ (5 mol %), TBAB (1 equiv), and Et_3N (2 equiv) was stirred in DMF (1 mL) at 120 °C for 1.5 h under the nitrogen protection until complete consumption of starting material as monitored by TLC and GC-MS analysis. After the reaction was finished, diethyl ether was poured into the mixture, then washed with water. The organic layer was dried with anhydrous Na_2SO_4 and evaporated under vacuum. The residue was purified by flash column chromatography (hexane/ethyl acetate) to afford the desired product **26** and **27**.

6-Bromo-5-phenyl-9*H*-pyrrolo[2,1-*e*]phenanthridine-2,7-dione (26). White solid, mp 247.2−249.3 °C (uncorrected); ^{1}H NMR (500 MHz) δ 7.53−7.51 (m, 1H), 7.45−7.37 (m, 5H), 7.33 (t, J = 4.0 Hz, 1H), 7.05−7.03 (m, 2H), 6.75 (d, J = 10.0 Hz, 1H), 6.40 (d, J = 2.0 Hz, 1H), 6.26−6.23 (m, 1H), 5.21 (d, J = 15.0 Hz, 1H), 4.18 (d, J = 15.5 Hz, 1H); ^{13}C NMR (125 MHz) δ 184.1, 171.3, 157.3, 150.7, 145.9, 136.1, 132.8, 131.5, 131.0, 130.0, 129.3, 129.1, 128.8, 128.6, 128.4, 126.2, 125.0, 121.1, 72.2, 44.9; IR (KBr, cm^{-1}) 1716, 1663; LRMS (EI 70 eV) *m*/z (%) 405 (M^+ + 2, 15), 403 (M^+, 14), 0.324 (39), 129 (100); HRMS (EI) for $C_{22}H_{14}{}^{79}BrNO_2$ (M^+) calcd 403.0208, found 403.0207.

6-Bromo-5-phenyl-1*H*-pyrrolo[2,1-*e*]phenanthridine-2,7(9*H*,13b*H*)-dione (27). White solid, mp 208.5−211.9 °C (uncorrected); ^{1}H NMR (500 MHz) δ 7.51−7.47 (m, 3H), 7.36−7.34 (m, 2H), 7.24−7.22 (m, 3H), 7.19−7.17 (m, 1H), 6.54 (d, J = 10.0 Hz, 1H), 6.23 (d, J = 10.0 Hz, 1H), 5.34 (d, J = 17.5 Hz, 1H), 4.38 (d, J = 17.5 Hz, 1H), 3.62 (s, 1H), 2.91 (d, J = 17.0 Hz, 1H), 2.27 (d, J = 17.0 Hz, 1H); ^{13}C NMR (125 MHz) δ 194.9, 163.5, 155.7, 143.5, 135.0, 132.3, 132.2, 131.4, 130.1, 129.2, 127.9, 127.3, 127.0, 126.6, 120.6, 100.0, 66.3, 41.5, 40.4, 39.2; IR (KBr, cm^{-1}) 1716, 1684; LRMS (EI 70 eV) *m*/z (%) 407 (M^+ + 2, 58), 405 (M^+, 56), 0.326 (100), 129 (74); HRMS (EI) for $C_{22}H_{16}{}^{79}BrNO_2$ (M^+) calcd 405.0364, found 405.0364.

Acknowledgment. We would like to thank the Specialized Research Fund for the Doctoral Program of Higher Education (No. 20060542007), National Natural Science Foundation of China (No. 20572020), and New Century Excellent Talents in University (No. NCET-06-0711) for financial support.

Supporting Information Available: General experimental procedures, characterization data for compounds **3**−**6**, **8**−**16**, and **18**−**28**, and copies of spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

JO8018297