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Spirocyclization |*Hot Paper*|

Hypervalent-Iodine-Mediated Cascade Annulation of Diarylalkynes Forming Spiro Heterocycles under Metal-Free Conditions

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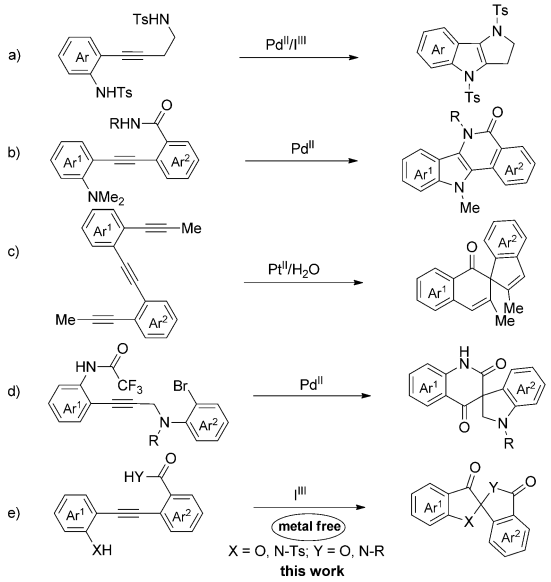
Abstract: An unusual reaction featuring the cascade annulation of internal alkynes to afford spiro heterocycles as the products has been realized for the first time with a hypervalent iodine reagent as the only oxidant. This unprecedented process encompasses not only two sequential C–N/C–O-bond formations, but also the insertion of a carbonyl oxygen, all in one pot under metal-free conditions.

Introduction

Cascade reactions,[1] during which multiple bonds, rings, or stereocenters are created in a single manipulation, have been extensively studied due to their unique applications in the assembly of complex molecular structures.[2] The cascade annulation of internal alkynes bearing aryl ring(s) is a useful synthetic strategy for the construction of bridged[3] or spiro[4] polycyclic rings. A literature survey reveals the following existing methods: 1) Pd^{II}/I^{III}-mediated intramolecular annulation of internal alkynes through successive C–N-bond formations (Scheme 1 a),[3a] 2) Pd^{II}-catalyzed intramolecular diamination of diarylacetylene accompanied by C(sp^3)–N bond cleavage to afford bioactive indoloisoquinolinones (Scheme 1 b),[3c] 3) Pt^{II}-catalyzed hydrative cyclization of trialkynes to form bicyclic spiro ketones (Scheme 1 c),[4a] and 4) Pd^{II}-catalyzed cascade reactions of alkyne intermediates leading to the construction of spiro[indoline-3,3′-quinoline] derivatives (Scheme 1 d).[4b] However, it is evident that all of the existing methods require the use of a transition-metal catalyst. To the best of our knowledge there is no report on conversions of diarylalkynes into the spiro heterocyclic skeleton in a cascade reaction under metal-free conditions. In this communication we report such a conversion, an unusual cascade annulation of diarylalkynes we recently discovered that affords spiro heterocyclic compounds under metal-free conditions with a hypervalent iodine reagent acting as the sole oxidant (Scheme 1 e).



Scheme 1. Cascade annulation reactions of internal alkynes.

Hypervalent iodine reagents, a class of environmentally benign, "green" non-metal oxidants, have experienced explosive development in oxidative annulation reactions.[5] A literature survey indicates that although iodine(III) and iodine(V) reagents have been widely used in various bond-forming reactions,[6] there are few examples of the construction of complex bridged or spiro heterocycles by efficient cascade processes.[7] Our continued interest in the search for novel applications of hypervalent iodine reagents for the construction of heterocycles has led us to investigate new reactions of diarylacetylenes with iodine(III) reagents.

The first reaction was carried out by treating **1 a**, a diarylacetylene, with 1.0 equivalent of phenyliodine diacetate (PIDA). A cascade process was observed and spiro compound **5 a** was afforded after 2 h in a yield of 31 % (Table 1, entry 1). The structure of the product was unambiguously confirmed by X-ray crystallography. Considering the fact that the construction of

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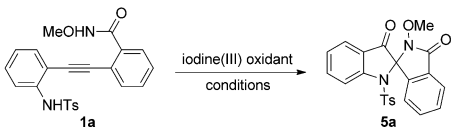
Table 1. Optimization of the reaction conditions for the iodine(III)-mediated cascade annulation reactions.[a]



Entry	Oxidant ([equiv])	Solvent	T [°C]	t [h]	Yield [%][b]
1	PIDA (1.0)	CH_2Cl_2	RT	2	31
2	PIDA (2.0)	CH_2Cl_2	RT	1	54
3	PIFA (2.0)	CH_2Cl_2	RT	0.5	62
4	PIFA (2.0)	THF	RT	1	49
5	PIFA (2.0)	CH_3CN	RT	2	42
6	PIFA (2.0)	DMF	RT	2	44
7	PIFA (2.0)	TFE	RT	1	39
8	PIFA (2.0)	TFA	RT	0.1	35
9[c]	PIFA (2.2)	CH_2Cl_2	RT	0.5	62
10[d]	PIFA (3.0)	CH_2Cl_2	RT	0.2	61
11	PhIO (2.0)	CH_2Cl_2	RT	12	20
12	PIFA (2.0)	CH_2Cl_2	−20 to 0	1	85
13	PIFA (2.0)	CH_2Cl_2	−50	5	82

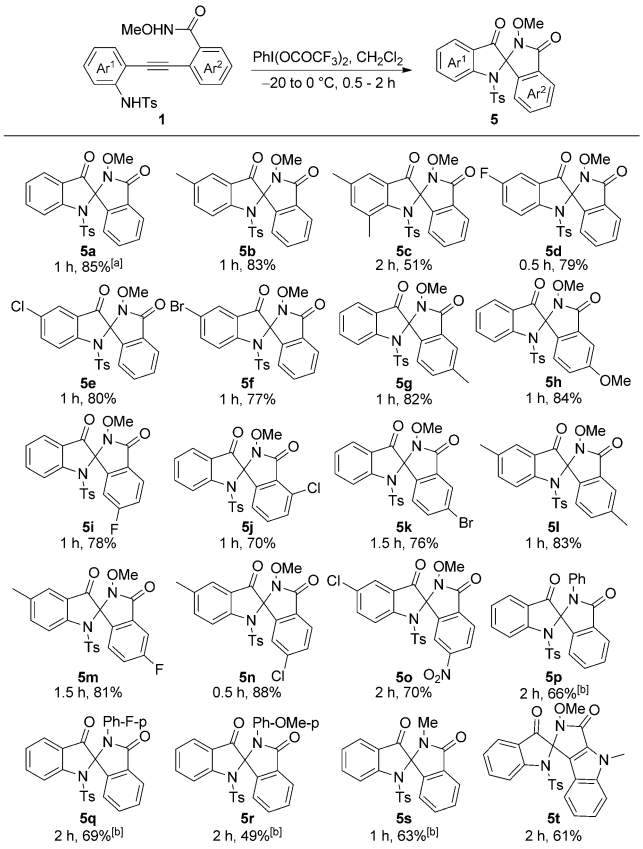
[a] Reagents and conditions: **1a** (0.2 mmol), oxidant (0.4 mmol), solvent (5 mL), unless otherwise stated. [b] Isolated yield. [c] 0.44 mmol of PIFA was used. [d] 0.60 mmol of PIFA was used.

this type of spiro skeleton was previously normally accomplished by the transannular reaction of eight-membered ring intermediates,[8] a procedure that is limited by the substitution pattern of the substrates, our initial success, albeit small, set the stage for a systematic search for a new approach that may be more efficient and/or broader in its application.

Results and Discussion

Diarylacetylene **1a** was used as the model substrate to screen for the optimal reaction conditions. The substrate was completely consumed when 2 equivalents of PIDA were employed, leading to an improved yield of 54% for the desired product (Table 1, entry 2). The replacement of PIDA by phenyliodine bis(trifluoroacetate) (PIFA) further improved the yield, albeit to a small extent (Table 1, entry 3). Solvent screening studies showed that none of the other solvents used, namely, THF, CH_3CN, DMF, TFE, and TFA, gave a higher yield than CH_2Cl_2 (Table 1, entries 4–8). An increased amount of PIFA also did not lead to any additional improvement in the yield (Table 1, entries 9 and 10). Another oxidant, PhIO, was tested, but this resulted in a much lower yield of the product (Table 1, entry 11). The reaction proceeded much more cleanly when the temperature was lowered to between −20 and 0 °C, giving a satisfying yield of 85% of the spiro product (Table 1, entry 12). Further lowering of the reaction temperature to −50 °C significantly lengthened the reaction time, and was accompanied by a slightly decreased yield (Table 1, entry 13).

A series of diarylacetylenes **1** were prepared (see the Supporting Information for details) to investigate the scope of the novel cascade annulation reaction under the optimized conditions (Scheme 2). First, we evaluated the electronic effects of substituents on the phenyl ring of the aniline moiety (Ar^1). An



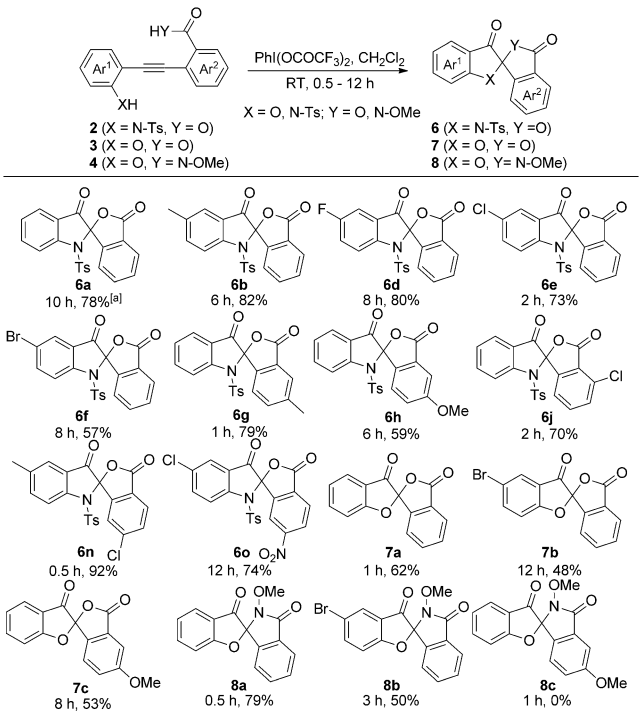
Scheme 2. $PhI(OCOCF_3)_2$-mediated oxidative cascade synthesis of spirocycles containing an N,N-ketal. All the reactions were carried out with substrate **1** (0.2 mmol) and PIFA (2.0 equiv) in CH_2Cl_2 (5 mL) at −20 to 0 °C. [a] Isolated yield. [b] Compound **6a** (for general structure, see Scheme 3) was isolated as a by-product (yield: 9, 7, 11, and 19% for **1p–s**, respectively).

electron-donating group displayed respectable suitability with the expected product obtained in a yield of 83% (Scheme 2, **5b**). Steric effects apparently hindered the conversion as the yield of **5c** was much lower. All halogen-substituted substrates were readily converted into the corresponding desired products in good yields (Scheme 2, **5d–f**). The electronic nature of the phenyl ring of the benzamide moiety (Ar^2) was also studied. The results show that electron-donating and -withdrawing substituents had no substantial impact on the efficacy of the reaction because the desired spiro compounds **5g–k** were all achieved in similar good yields. Steric hindrance was again observed in the case of **1j**, as demonstrated by the lower yield relative to the other substrates (Scheme 2, **5j**). Substrates bearing one substituent on both Ar^1 and Ar^2 were also transformed into the target compounds in similar satisfactory yields (Scheme 2, **5l–o**). We then replaced the OMe group in the parent **1a** by an aryl or alkyl group (**1p–s**); all the anticipated products were obtained in moderate yields (Scheme 2, **5p–s**). In addition, the indole derivative **1t** was successfully transformed into the desired product **5t** in a yield of 61% (Scheme 2).

Three important observations need to be addressed. First, spiro[indoline-2,1′-isobenzofuran]-3,3′-dione (**6a**) was isolated

as a by-product in yields of 7–19% from substrates **1p–s**. Secondly, although *N*-methyl amide **1s** was transformed into the desired product **5s** in a similar fashion, the *N*-unsubstituted amide (not given) was completely converted into **6a** in a yield of 88%. Thirdly, no desired product was obtained when the tosyl group was replaced by a benzyl group. This last observation suggests that the electron-withdrawing substituent on the nitrogen atom of the aniline moiety is crucial for the reaction.

Encouraged by the above findings, we expanded the range of substrates to three additional series: **2** (X = N-Ts, Y = O), **3** (X = O, Y = O), and **4** (X = O, Y = N-OMe). The novel cascade reaction strategy was shown to be applicable to all three series of diaryacetylenes (Scheme 3). For substrates **2** bearing either electron-donating or -withdrawing substituents on Ar^1, the corresponding spiro[indoline-2,1′-isobenzofuran]-3,3′-diones **6**

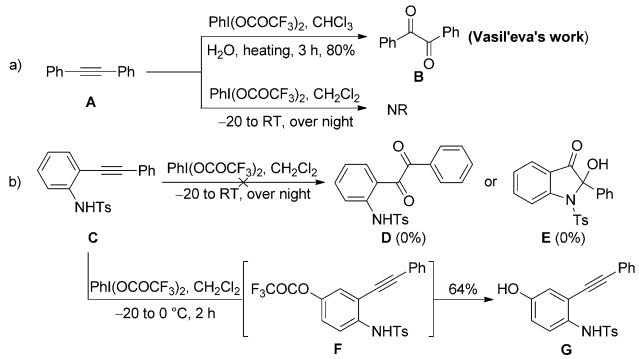


Scheme 3. $PhI(OCOCF_3)_2$-mediated oxidative cascade synthesis of spirocycles containing an N,O- or O,O-ketal. All the reactions were carried out with substrates (0.2 mmol) and PIFA (2.2 equiv) in CH_2Cl_2 (5 mL) at room temperature. [a] Isolated yield.

were formed in a similar efficient fashion with the exception of the bromo-substituted **6f**, which was obtained in a relatively low yield. Concerning the substituent effect on Ar^2, the methyl- and chloro-substituted substrates **2g** and **2j**, respectively, underwent the cascade annulation process more smoothly and efficiently than the methoxy-substituted **2h** (Scheme 3, **6g**, **6h**, and **6j**). Moreover, substrates bearing one substituent on both Ar^1 and Ar^2, namely, **2n** and **2o**, also gave good yields of the corresponding spiro products (**6n** and **6o**).

Compounds **3** underwent the expected annulation reactions smoothly and afforded the corresponding spiro[benzofuran-2,1′-isobenzofuran]-3,3′-dione derivatives **7a–c** in moderate yields. As for the phenol-amides **4**, the unsubstituted **4a** and the bromo-substituted **4b** were both successfully converted into the spiro[benzofuran-2,1′-isoindoline]-3,3′-diones **8a** and **8b** in yields of 79 and 50%, respectively. Disappointingly, the methoxy-functionalized **4c** did not give the desired product under the standard conditions.

Having established the scope of the method, we also studied the mechanism of the reaction (Scheme 4). Taking into account the fact that alkynes can be converted into diketones under the conditions of Vasil'eva and co-workers,[9] we first subjected diphenylacetylene (**A**) to our oxidative conditions.

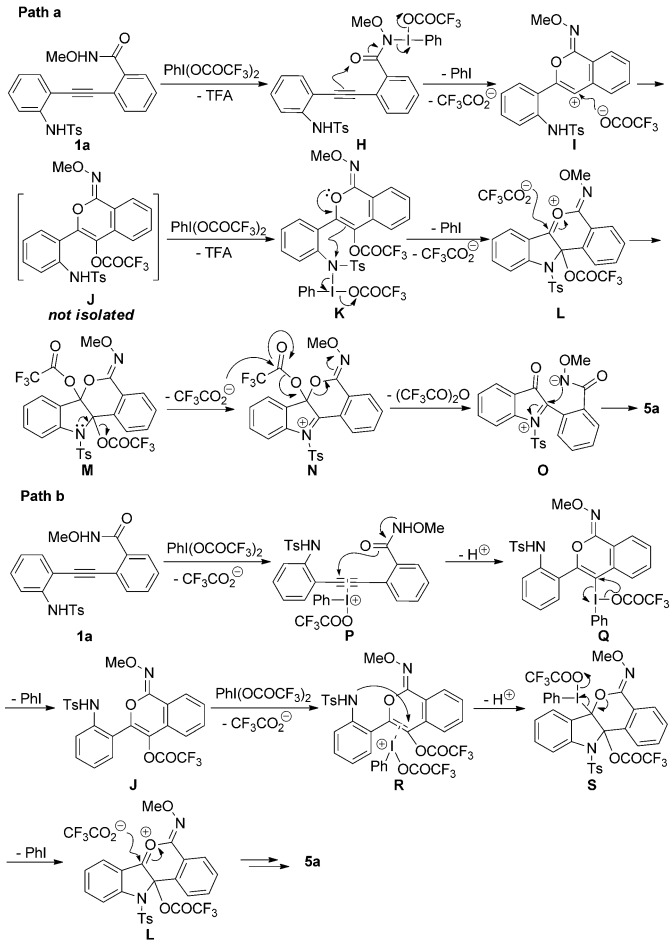


Scheme 4. Reactions undertaken as part of the mechanistic study.

No reaction occurred in the presence of PIFA in CH_2Cl_2 overnight, which excludes the diketone-type mechanism (Scheme 4a). In addition, the oxidation of diarylacetylene **C** under the optimal conditions only generated aryl-functionalized products **F** and **G** instead of diketone **D** or 2-hydroxyindolin-3-one **E**, which provides further evidence for the stability of the triple bond and tosyl group under the described conditions (Scheme 4b).[10]

A plausible mechanism was then proposed for the cascade annulation reaction and is depicted in Scheme 5 using compound **1a** as an example. In path a, intermediate **H**, initially formed from the reaction between **1a** and PIFA, accompanied by the loss of one molecule of trifluoroacetic acid,[11] gives rise to the cationic intermediate **I** after intramolecular C–O-bond formation and the release of one molecule of iodobenzene and the trifluoroacetate anion. Then an energetically downhill process involving the combination of the negatively charged trifluoroacetate and the positively charged carbon center in **I** furnishes the key intermediate **J**.[12] Oxidation of the tosylamide moiety,[13] accompanied by the loss of another molecule of trifluoroacetic acid, provides intermediate **K**, which undergoes intramolecular indolization to generate intermediate **L**. Another nucleophilic attack by a trifluoroacetate anion on the most electrophilic carbon in **L** results in the formation of intermediate **M**, which is converted into the iminium **N**. Promoted by the release of the trifluoroacetate anion, ring-opening occurs in intermediate **N** to furnish iminium **O**, which undergoes rapid cyclization to provide the title spirocyclic compound **5a**.

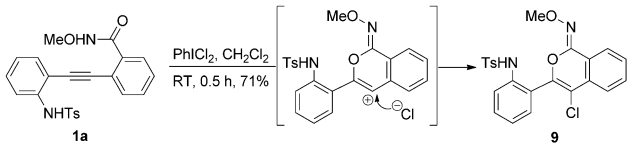
A possible alternative path b begins with the activation of the triple bond by PIFA to give electrophilic intermediate **P**,[14]



Scheme 5. Plausible mechanistic pathways for the cascade annulation reaction.

which then reacts with the nucleophilic benzamide to generate intermediate **Q**. The release of one molecule of iodobenzene from **Q** affords the same intermediate **J**. Another electrophilic intermediate **R**, formed by further activation of the internal double bond by PIFA, gives rise to intermediate **S** after the final cyclization by an intramolecular electrophilic reaction. By cleavage of the C–I bond and the release of another molecule of iodobenzene, intermediate **S** was converted into oxonium **L**. The final product **5a** was obtained from **L** by a similar process to that depicted in path a. This mechanism very reasonably accounts for the transformation of compounds **3** and **4** shown in Scheme 3.

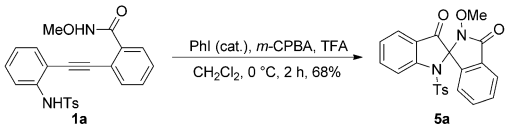
To verify the proposed mechanisms, we attempted to capture the key intermediate **J**, but unfortunately, because the reaction proceeded too quickly, no significant amount of any of the intermediates could be isolated during the course of the reaction. However, we managed to capture the isochromen-1-one derivative **9** (71% yield) after replacing PIFA by $PhICl_2$ in the reaction of **1a** (Scheme 6). The structure of **9** was unambiguously confirmed by X-ray crystallography. Although intermediate **J** was not directly observed during the reaction, the isolation of **9** in a parallel reaction of substrate **1a** provides convincing evidence for the proposed reaction pathway involving intermediate **J**.[15] Also, taking into consideration the influence of residual water in the reaction system, we carried out another control reaction by employing 4 Å molecular sieves and found that **5a** was achieved in exactly the same yield (83%). This indicates that the source of oxygen was indeed the oxidant PIFA, consistent with the proposed mechanistic pathways.



Scheme 6. Cascade annulation reaction of internal alkyne **1a**.

The mechanism proposed in path a of Scheme 5 effectively accounts for the steric hindrance of the *ortho* substituent on Ar[1], for its ability to impede the approach of PIFA during the formation of intermediate **K** from **J**. The mechanism also sheds light on the role of the electron-withdrawing nature of the tosyl group, because during the indolization step from intermediate **K** to **L**, the nitrogen to which the tosyl is attached needs to be sufficiently electrophilic.

It is worth noting that the described transformation could also be realized through an organocatalytic oxidative pathway[16] by using PhI as the catalyst and *m*-chloroperbenzoic acid (*m*-CPBA) as the terminal oxidant (Scheme 7).[17] Furthermore, when the reaction of **1a** was performed in the presence of chiral iodine(III) reagents, no enantioselectivity was observed[18] (see the Supporting Information for details), in agreement with the proposed mechanism in which the intramolecular cyclization occurring in **O** in the final stage cannot introduce enantioselectivity.



Scheme 7. Organocatalyzed formation of the spiro product **5a**.

Conclusion

We have discovered a new approach to the construction of a series of structurally novel spiro compounds from di-*ortho*-substituted diarylacetylenes through an unusual hypervalent-iodine-mediated cascade annulation process. This is the very first report of a complex spirocyclization of alkyne substrates under metal-free conditions involving two bond formations and one oxygen insertion in the form of a cascade reaction. The proposed mechanism provides sound explanations for many of the observations made during studies of substituent and steric effects.

Experimental Section

CCDC 1037460 (**5a**) and 1037461 (**9**) contain the supplementary crystallographic data for this paper. These data can be obtained

free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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Keywords: annulation · domino reactions · hypervalent iodine · reaction mechanisms · spiro compounds

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FULL PAPER

Metal-free spirocycles: An unusual reaction featuring the cascade annulation of internal alkynes to afford spiro heterocycles as the products has been realized for the first time with a hypervalent iodine reagent as the only oxidant (see scheme). This unprecedented process encompasses not only two sequential C–N/C–O-bond formations, but also the insertion of a carbonyl oxygen, all in one pot under metal-free conditions.

Spirocyclization

*X. Zhang, C. Yang, D. Zhang-Negrerie, Y. Du**

■■ – ■■

Hypervalent-Iodine-Mediated Cascade Annulation of Diarylalkynes Forming Spiro Heterocycles under Metal-Free Conditions