Chemoselective and Regioselective Synthesis of Spiroisoindolinone Indenes *via* an Intercepted Meyer-Schuster Rearrangement/Intramolecular Friedel-Crafts Alkylation Relay

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ABSTRACT: A Brønsted acid-catalyzed reaction between isoindolinone-derived propargylic alcohols and external aromatic nucleophiles for the construction of spiroisoindolinone indenes is described. The reaction proceeds rapidly with a broad range of substrates to generate spiroindenes chemoselectively and regioselectively in moderate to high yields. Key to the success of this transformation is an intercepted Meyer-Schuster rearrangement/intramolecular Friedel-Crafts alkylation relay that offers modular approach in the synthesis of target compounds.

Past several decades has witnessed the development of numerous strategies for the synthesis of structurally divergent spiroisoindolinones.1 Among those, only a handful of reported strategies tackle the synthesis of spiroisoindolinone indenes, which predominantly rely on transition-metal catalyzed annulation reactions (Scheme 1).

Seminal reports by Grigg et al exploit regiospecific intramolecular Heck reaction of *N*-vinyl amide derivatives of 2-iodobenzoic acid to construct spiroisoindolinone indene unit.2 More recently, Nishimura reported [3+2] cyclization between *in* *situ* generated ketimines and terminal or internal alkynes catalyzed by cationic iridium complex.3 In a similar fashion, rhodium-catalyzed [3+2] annulation of cyclic *N*-acyl ketimines with acrylates and quinones followed by Prins-type reaction afforded spiroisoindolinone indenes.4 In this context, it is also worth mentioning rhodium-catalyzed [3+2] annulation of cyclic *N*-sulfonyl ketimines with alkynes to access spirocyclic benzosultamindenes in both racemic5 and enantioselective fashion.6 In addition, the intermediate formed by annulation of *N*-sulfonyl ketimine and alkyne can be trapped by an aldehyde to form polycyclic skeleton comprising sultam indene moiety. Wu et al developed an interesting rhodium catalyzed redox-neutral cascade reaction between benzamides and cyclopropenones. Reaction proceeds through C-H activation followed by addition to polar carbonyl group to assemble cyclopentene spiroisoindolinones.7

On the other hand, metal-free approaches are virtually non-existent in the literature. Within a broader study, Hauser et al demonstrated that spiroisoindolinone indenes can be obtained by dehydration and intramolecular cyclization of fluorenyl-derived benzamide tertiary alcohols mediated by perchloric acid.8 To the best of our knowledge, the first systematic study was reported by Wang and Lu.9 Their work represents an elegant one-pot conversion of hydroxypropynyl benzonitriles to spiroisoindolinone indenes *via* a sulfuric acid-mediated cyclization.

Scheme 1. Strategies towards spiroisoindolinone indenes.



Although strategies based on C-H activation are appealing as they eliminate the need for sometimes tedious interconversion of various functionalities, the necessity to use low abundant transition metals – together with their associated cost and requirement for specific handling techniques – often deters one from implementing them in specific synthetic designs. Moreover, methods that employ unsymmetrical alkynes are often accompanied by poor regioselectivity. Thus, development of a reliable method that would improve on these shortcomings, and at the same time allow controllable chemoselectivity and regioselectivity is highly desirable.

Herein we report the strategy towards spiroisoindolinone indenes based on sequential intercepted Meyer-Schuster rearrangement10/Intramolecular Friedel-Crafts alkylation relay. Inspired by Chatterjee’s synthesis of indene derivatives *via* Brønsted acid-catalyzed transformation of tertiary propargylic alcohols in the presence of electron rich aromatic rings,11 we envisioned a similar approach with specifically designed precursors which would allow the construction of spiroisoindolinone indenes. The molecular diversity in the final products is achieved through differently substituted isoindolinone units, preassembled in two steps from commercially and readily available phthalimides.

We started our investigations by combining 3-hydroxy-2-methyl-3-(phenylethynyl)isoindolinone **Is-1** with 1,3,5-trimethoxybenzene in the presence of various Brønsted acids in acetonitrile at 80 °C (Table 1, full screening in the Supporting Information).

Table 1. Screening of reaction conditions.a



|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| entry | catalyst  | solvent | T/°C | time/h | yield/% |
| 1 | PhCOOH | acetonitrile | 80 | 21 | >96 |
| 2 | DPPb | acetonitrile | 80 | 21 | >96 |
| 3 | *p*-TsOH | acetonitrile | 80 | 3 | 84 |
| 4 | PPAc | acetonitrile | 80 | 21 | - |
| 5 | AcOH | acetonitrile | 80 | 24 | - |
| **6** | **MsOH** | **acetonitrile** | **80** | **0.25** | **>96** |
| 7 | TFA | acetonitrile | 80 | 24 | 83 |
| 8 | MsOH | cyclohexane | 80 | 24 | - |
| 9 | MsOH | toluene | 80 | 24 | - |
| 10 | MsOH | ethanol | 80 | 24 | - |
| 11 | MsOH | ethyl acetate | 80 | 24 | 51 |
| 12 | MsOH | acetonitrile | 40 | 3.5 | >96 |
| 13 | MsOH | acetonitrile | 60 | 1.5 | >96 |

*a*Reactions performed on a 0.2 mmol scale. Product confirmed by 2D NMR. *b*Diphenyl phosphate. *c*Phenylphosphinic acid.

In a reaction catalyzed by benzoic acid, product **1** was obtained in almost quantitative yield after 21 hours (entry 1), and a similar trend was observed with diphenyl phosphate (entry 2). By employing *p*-toluenesulfonic acid as a catalyst, the reaction was completed after 3 hours, however, albeit with a slight drop in yield (entry 3). On the other hand, no product was detected in reactions catalyzed by phenylphosphinic acid or acetic acid, respectively (entries 4 and 5). When methanesulfonic acid was used as a catalyst, the reaction was completed within 15 minutes, and product **1** was isolated in >96% yield (entry 6). The reaction was also successfully catalyzed by trifluoroacetic acid (entry 7).

Next, we investigated the influence of the solvent and temperature on the reaction outcome. By conducting the reaction in cyclohexane and toluene, only starting materials were detected in the reaction mixture after 24 hours (entries 8 and 9). The reaction in ethanol resulted with complex mixture of products (entry 10), while reaction times were prolonged and yields diminished by conducting the transformation in ethyl acetate (entry 11). Lowering the reaction temperature did not influence the reaction yield, though it considerably slowed down the conversion rate. Hence, out of the screened reaction conditions, the best performance was obtained by using isoindolinone-derived propargylic alcohol (1.0 eq), phenol derivative (1.0 eq), and methanesulfonic acid (10 mol%) in acetonitrile at 80 °C, and this set of conditions was used in further experiments.

With established reaction conditions in hand, we turned our attention to investigate the substrate scope and reaction limitations (Table 2).

Table 2. Substrate scope I: Isoindolinones.a



*a*Reactions conditions: Propargylic alcohol (0.1 or 0.2 mmol), 1,3,5-trimethoxybenzene (1.0 equiv), MsOH (10 mol%) in CH3CN (0.1M solution) at 80 °C.

In addition to *N*-methyl group, aliphatic *N*-isopropyl and *N*-benzyl groups were also well tolerated under the used reaction conditions, and cyclization products **2–5** were formed in moderate to high yields. In a similar fashion, spiroindenes **6** and **7** bearing *N*-phenyl, and *ortho*-substituted *N*-phenyl ring were obtained in 95% and 96% yield, respectively. The reaction yield decreased when *N*-naphthyl substituted isoindolinone alkyne was used (**8**). As expected, the steric impact of the *para*-methoxy group on the *N*-phenyl ring was negligible, and the products **9** and **10** were isolated in high yields. Reactions with *meta* substituents on the *N*-aromatic ring proceeded uneventfully to yield desired products **11** and **12**.

Then our attention turned to various *para*-substituted phenyl rings on the alkyne. The reaction with starting alcohol bearing chlorine atom in this position provided spiroindene product **13**. Likewise, *para*-methyl group had also no effect on the course of the reaction (**14** and **15**). On the other hand, product **16** was isolated in moderate yield, most likely due to the deactivation of *meta* position (with respect to methoxy group) through which the cyclization occurs.

The reaction with isoindolinone derivative bearing *meta*-methyl group on the phenyl substituent on the alkyne resulted in the inseparable mixture of two regioisomers **17**/**17'** in 2:1 ratio, with reaction favoring sterically less crowded regioisomer **17**. It seems that *ortho*-methyl group imposes noticeable steric hindrance, thus allowing the formation of several unidentified side-products and hampering smooth cyclization that leads to target product **18**. Finally, placing substituents on the phenyl ring of the isoindolinone core did not change the reaction outcome (**19**).

Furthermore, we turned our attention to investigate the scope and limitations of the reaction with various external nucleophiles (Table 3). When 1-naphthol was employed as a nucleophile, addition to alkyne occurred through *para* position (with respect to hydroxy group), thus yielding product **20**. High regioselectivity was also observed with veratrol, and product **21** was isolated in 38% yield. 2,6-dimethyl phenol was successfully employed as well, and as in two previous examples, the cyclization occurred chemoselectively through more electron-rich aromatic ring (**22** and **23**). It is worth mentioning that electron density in unsubstituted phenol was too low to initiate the addition to the alkyne and to intercept the Meyer-Schuster rearrangement.12

Next, 1-naphthol and isoindolinone-derived propargylic alcohol bearing (3,5-dimethoxy)phenyl substituent on the alkyne were submitted to standard reaction conditions. Although both aromatic rings are electron-rich and competitive intramolecular Friedel-Crafts reactions can occur, only product **24** was isolated from the reaction mixture. This result demonstrates the utility of the developed method, where difference in the distribution of electron density in respective aromatic rings controls the chemoselectivity of the cyclization. When 2,6-dimethoxyphenol was employed, the formation of two regioisomers was observed. The combined *ortho*-*para* directing effect of two methoxy groups overpowers the electron donating ability of the hydroxy group, thus affecting the regioselectivity of the the initial addition to alkyne. Hence, products **25/25'** (1.5:1 regioisomeric ratio) and **26/26'** (1.4:1 regioisomeric ratio) were isolated as inseparable mixtures of respective spiroindenes.

When orcinol was submitted to standard reaction conditions, spiroisoindolinone-derived 2*H*-chromene **27** was isolated in 74% yield as a result of cyclization through hydroxy group. This type of heterocyclization was also observed in cascade reactions between tertiary propargylic alcohols and electron-rich phenols.13 Chromene derivative **28** was also obtained when sesamol was employed as an external nucleophile. Interestingly, chromene type of product (**29**) was isolated as the sole product in the reaction with 2-(dimethylamino)phenol, although cyclization could have occurred through sterically non-hindered position on the aromatic ring. Since this position lies in *meta* position with respect to two highly *meta*-deactivating groups, competitive *O*-alkylation obviously occurs faster than C-C bond formation leading to spiroindene product. The competitive heterocyclization was suppressed in the reaction between sesamol and isoindolinone-derived propargylic alcohol bearing electron-rich (3,5-dimethoxy)phenyl substitutent, and only product **30** was detected and isolated from the reaction mixture.

Table 3. Substrate scope II: External nucleophiles.a



*a*Reactions conditions: Propargylic alcohol (0.1 or 0.2 mmol), phenol derivative (1.0 equiv), MsOH (10 mol%) in CH3CN (0.1M solution) at 80 °C. Products confirmed by 2D NMR (see Supporting Information for details). *b*Reaction carried out with *p*-TsOH (10 mol%).

Finally, reactions with other external nucleophiles were investigated.14 When indole was employed, only product **31** was isolated from the reaction mixture. On the other hand, reaction with 2,5-dimethylpyrrole resulted in the cyclized product **32**. These results suggest that there is an upper limit in the strength of the nucleophile after which the addition starts to occur on the C3-position of the isoindolinone ring, rather than on the alkyne.

While monitoring the progress of the reaction by TLC, the formation of a particular intermediate was observed in most examples, which was gradually converted to spiroindene product during the course of the reaction. Under the standard reaction conditions, observed intermediate was too quickly consumed to be isolated for full characterization. Hence, the reaction catalyzed by *para*-toluenesulfonic acid at 25 °C was performed, and intermediate **1*i*** was succesfully isolated in >96% yield, and its structure was confirmed by X-ray structure analysis (Scheme 2). When submitted to elevated temperature in the presence of the catalytic amount of *para*-toluenesulfonic acid, intermediate **1*i*** underwent rapid cyclization to yield spiroindene **1**.

Scheme 2. Control experiments.



Finally, in addition to the successful scale-up reaction (Table 2, **1**), we explored possibilities for the utilization of obtained products in further transformations (Scheme 3). The reduction of amide group in product **1** was successfully performed with lithium aluminum hydride, yielding isoindoline derivative **33** in very good yield. Bromination of indene ring in **1** was achieved with *N*-bromosuccinimide, though product **34** was isolated as inseparable mixture with double-bromination side-product **35**.

Scheme 3. Postmodification reactions.



With the obtained information, we are able to propose a plausible mechanism for the cascade reaction (Scheme 4). Although depicted for the formation of product **1**, the mechanism applies to all other examples resulting in the formation of spiroisoindolinone indenes regardless of the chemoselectivity and regioselectivity of the cyclization step. Following the protonation of isoindolinone-derived propargylic alcohol, water molecule is eliminated to generate a highly reactive ketimine intermediate **A** (evidenced by the formation of **31**). The presence of an external nucleophile intercepts Meyer-Schuster rearrangement to generate allene amide intermediate **B**. The protonation of allene leads to the formation of ketiminium species **C** and **C'**. Because of its favourable configuration, **C** can undergo intramolecular Friedel-Crafts alkylation to yield target product. On the other hand, **C'** can either react reversibly with water molecule to generate intermediate **1*i***, or can rotate aryl rings into favorable position for the cyclization while in its resonance structure **D**.

Scheme 4. Proposed reaction mechanism.



In conclusion, we have developed a Brønsted acid-catalyzed reaction between isoindolinone-derived propargylic alcohols and external aromatic nucleophiles for the chemoselective and regioselective preparation of spiroisoindolinone indenes. This cascade process, which encompasses an intercepted Meyer-Schuster rearrangement/intramolecular Friedel-Crafts alkylation relay, offers a rapid modular approach to highly functionalized scaffolds that may find application as frameworks in the synthesis of natural product analogues.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Detailed procedures, NMR spectra, list of starting isoindolinone-derived propargyl alcohols (**Is-1–Is-18**), complete screening of reaction conditions, 2D NMR experiments (PDF), X-ray crystallography.

FAIR Data is available as Supporting Information for Publication and includes the primary NMR FID files for compounds in the manuscript **(1-35**) and in the SI (**Is-1–Is-19, 36**). See FID for Publication for additional information.

Notes
The authors declare no competing financial interest.

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