Solvent-dependent chemoselective synthesis of different isoquinolinones mediated by the hypervalent iodine(III) reagent PISA

Ze-Nan Hu‡, Yan-Hui Wang‡, Jia-Bing Wu, Ze Chen, Dou Hong and Chi Zhang*

Abstract
Isoquinolinone is an important heterocyclic framework in natural products and biologically active molecules, and the efficient synthesis of this structural motif has received much attention in recent years. Herein, we report a (phenyliodonio)sulfamate (PISA)-mediated, solvent-dependent synthesis of different isoquinolinone derivatives. The method provides highly chemoselective access to 3- or 4-substituted isoquinolinone derivatives by reacting o-alkenylbenzamide derivatives with PISA in either acetonitrile or wet hexafluoro-2-isopropanol.

Introduction
Isoquinolinone is an important heterocyclic structure found in many natural products and biologically active compounds, including pharmaceuticals [1]. For instance, lycoricidine, a component of lycoris radiata, may inhibit the MCPyV LT protein activity and thus block cancer formation [2]. Alangiumkaloids A, an isoquinolinone alkaloid isolated from Alangium salviifolium, was reported to exhibit cytotoxic activity against cancer cells [3]. In 2018, duvelisib, a dual inhibitor of phosphoinositide-3 kinases, was firstly approved by the FDA for the treatment of adult patients with relapsed or refractory chronic lymphocytic leukaemia or small lymphocytic lymphoma [4]. Palonosetron is a key component of Akynzeo®, used for the prevention of acute and delayed nausea and vomiting of cancer patients who are receiving chemotherapy [5]. As an active compound, PF-06821497 showed potent tumor growth inhibition in mouse xenograft models [6]. CRA-680 was efficacious in both a house dust mouse model of allergic lung inflammation and a guinea pig allergen challenge model of lung inflammation [7]. In addition, isoquinolinone compounds not only prevent and control plant diseases but also have some
herbicidal activity. Compound I showed good inhibitory activity against *Sclerotinia sclerotiorum* on detached oilseeds of rape leaves [8], and compound II has excellent herbicidal activity against dicot weeds, such as *Zinnia elegans* Jacq. and *Abutilon theophrasti* Medicus (Figure 1) [9]. Therefore, in recent years, isoquinolinone derivatives have attracted considerable attention, and successful synthetic methods involving the isoquinolinone framework have been reported.

A number of appealing methods for the synthesis of isoquinolinone scaffolds using transition metal reagents, including cobalt [10], copper [11], rhodium [12-14], palladium [15-17], silver [18], and gold [19] catalysts, have been reported. However, compared to the widespread use of metal catalysts, the synthesis of isoquinolinone scaffolds mediated by environmentally friendly nonmetallic reagents as an attractive alternative is less developed. In 2014, Antonchick and Manna firstly reported the synthesis of a series of 3,4-diaryl-substituted isoquinolinone derivatives through oxidative annulation between alkynes and benzamide derivatives using iodobenzene as a catalyst and peracetic acid as a terminal oxidant [20]. Recently, Kočovský et al. disclosed a method employing 2-methylbenzamide and benzonitrile to yield 3-aryl-substituted isoquinolinone derivatives in the presence of *n*-butyllithium [21]. On the other hand, the intramolecular oxidative cyclization is also a viable option for the preparation of isoquinolinone derivatives. In 2020, two reports have been published on the conversion of alkyne-tethered *N*-alkoxybenzamides to isoquinolinones by intramolecular oxidative annulation, either electrochemically or using the hypervalent iodine reagent phenyliodine(III) diacetate (PIDA) [22,23]. And more recently, Du and our group have developed a method for the chemoselective cycloisomerization of *o*-alkenylbenzamides to 3-arylisoquinolinones, using PhIO as oxidant in combination with a catalytic amount of trimethylsilyl trifluoromethanesulfonate [24]. Although considerable progress has been made in the synthesis of isoquinolinone derivatives, there is still the need to develop chemoselective strategies based on easily adjustable factors, such as solvent selection to obtain 3- or 4-substituted isoquinolinone derivatives.

In 2018, our group has reported the zwitterionic water-soluble hypervalent iodine reagent (phenyliodonio)sulfamate (PISA). In water, PISA is strongly acidic, and the pH value can reach 2.05 in a saturated aqueous solution. With PISA, various indoles have been synthesized via C–H amination of 2-alkenylanilines involving an aryl migration–intramolecular cyclization cascade with excellent chemoselectivity in aqueous CH₃CN [25]. Herein, as part of our continuing studies of heterocyclic scaffold synthesis mediated by hypervalent iodine reagents, we present the solvent-dependent chemoselective synthesis of a series of isoquinolinones mediated by PISA using 2-alkenylbenzamide derivatives as substrates (Scheme 1).

**Results and Discussion**

We began by exploring the reaction of *N*-methoxy-2-(prop-1-en-2-yl)benzamide (1a) with PISA (1.5 equiv) in anhydrous acetonitrile at room temperature under argon atmosphere. 4-Methylisoquinolinone 2a was the sole product in the reaction, with a yield of 86% in 20 minutes (Table 1, entry 1). Encouraged by this result, we added additives to the reaction with the aim of further increasing the chemical yield of 2a. When 1.5 equivalents of water were added to the reaction, the yield of 2a dropped to 79% (Table 1, entry 2). The reduced yield of 2a indicated that this reaction could benefit from a dry solvent.
Scheme 1: Chemoselective and PISA-mediated, solvent-controlled synthesis of different isoquinolinone derivatives 2 and 3.

Therefore, 4 Å molecular sieves or anhydrous sodium sulfate were added to the reaction mixture. When 4 Å molecular sieves were added, the yield of 2a slightly increased to 88%, which was superior to using Na₂SO₄ (Table 1, entries 3 and 4). Next, different commercially available iodanes were employed as oxidants, such as PIDA, phenyliodine(III) bis(trifluoroacetate) (PIFA), N-tosyliminobenzylodinane (PhINTs), iodosylbenzene (PhIO), and Koser’s reagent (HTIB) (Table 1, entries 5–9). Of the reagents tested, PISA gave the best result. Furthermore, screening of different solvents showed that acetonitrile was superior for this reaction (Table S1, Supporting Information File 1). Based on the screening results, the optimized reaction conditions for the conversion of 1a to the 4-substituted isoquinolinone 2a were as follows: 1.5 equivalents of PISA and 4 Å MS in anhydrous CH₃CN (0.1 M of 2a) under argon atmosphere at room temperature for 20 min.

Table 1: Optimization of the reaction conditions for the synthesis of 4-substituted isoquinolinone 2a.

<table>
<thead>
<tr>
<th>entry</th>
<th>iodane</th>
<th>additive</th>
<th>yield of 2a, %b</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>PISA</td>
<td>—</td>
<td>86</td>
</tr>
<tr>
<td>2</td>
<td>PISA</td>
<td>H₂O (1.5 equiv)</td>
<td>79</td>
</tr>
<tr>
<td>3</td>
<td>PISA</td>
<td>4 Å MS</td>
<td>88</td>
</tr>
<tr>
<td>4</td>
<td>PISA</td>
<td>Na₂SO₄</td>
<td>81</td>
</tr>
<tr>
<td>5</td>
<td>PIDA</td>
<td>4 Å MS</td>
<td>52</td>
</tr>
<tr>
<td>6</td>
<td>PIFA</td>
<td>4 Å MS</td>
<td>77</td>
</tr>
<tr>
<td>7</td>
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<td>4 Å MS</td>
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<tr>
<td>9</td>
<td>HTIB</td>
<td>4 Å MS</td>
<td>52</td>
</tr>
</tbody>
</table>

aReactions were carried out using 1a (0.2 mmol), hypervalent iodine reagent (1.5 equiv), and 4 Å MS (7.6 mg) in MeCN (2.0 mL) at room temperature under argon atmosphere. bIsolated yield.

With the optimal reaction conditions in hand, we explored the scope of the method by testing various 2-alkenylbenzamide derivatives 1 (Scheme 2). When R¹ was ethyl, isopropyl, cyclopropyl, phenyl, or hydrogen, respectively, the intramolecular amination smoothly gave the corresponding 4-substituted isoquinolinone products 2b–f in 51–94% yield. Notably, when 1c was used as the substrate, the cycloisomerization product 2c’ was observed in 31% yield besides 2c in 51% yield. Additional experiments were then carried out using N-methoxy-2-(prop-1-en-2-yl)benzamide with different substituents R². Both electron-donating (methyl, alkoxy, dimethylamino) and electron-withdrawing substituents (fluoro, chloro, trifluoromethyl) were well tolerated on the phenyl ring and gave the desired products 2g–n in 68–95% yield. Furthermore, a substrate containing a naphthalene moiety was also compatible with the reaction conditions, giving the corresponding ring-fused product 2o in 40% yield. It is worth noting that when the N-substituent was phenyl, benzyloxy, or phenylamino, the reaction still proceeded well, and the corresponding products 2p–r were obtained in 69%, 41%, and 40% yield, respectively.

Interestingly, when screening solvents for the synthesis of 4-methylisoquinolines, we were surprised to discover that when hexafluoro-2-propanol (HFIP) was used as the solvent, 3-methylisoquinolinone 3a, an isomer of 2a, was formed in 51% yield. Apparently, the change of solvent resulted in a different chemoselectivity of the reaction. With this in mind, we investigated the reaction conditions (see Supporting Information File 1 for details) and obtained the optimal conditions for the synthesis of 3-methylisoquinolinone as follows: reacting 1.1 equivalents of PISA in HFIP (0.1 M of 1a) containing 2.5 equivalents of H₂O at room temperature for 20 minutes (Scheme 3).
Scheme 2: Substrate scope for the synthesis of 4-substituted isoquinolinones 2. Reaction conditions: 1 (0.3 mmol), PISA (1.5 equiv), and 4 Å MS (10 mg) in MeCN (3.0 mL).

The general applicability of PISA in wet HFIP solvent was studied. When R¹ was ethyl, isopropyl, cyclopropyl, or hydrogen, respectively, the substrates could be successfully converted to the products 3b–d and 2f in 52–87% yield with this method. In addition, a good or high yield of 3-methylisoquinoliones 3e–k, with different substituents on the phenyl ring, was also obtained. It is worth noting that when an electron-withdrawing group (trifluoromethyl, fluoro, chloro) was located on the phenyl ring, various amounts of 4-substituted isoquinolione derivatives 2k,m,n were observed along with the formation of 3h,j,k, respectively. Furthermore, a substrate containing a naphthalene unit was also compatible with the reaction conditions, leading to 3l. In particular, the presence of diverse nitrogen protecting groups, such as benzyloxy, phenyl, and...
Scheme 3: Optimal reaction conditions for the synthesis of 3-substituted isoquinolinone 3a. Alkyl, did not affect the smooth reaction, affording 3m-o in a moderate yield of 32–64% (Scheme 4). Just by changing the solvent of the reaction, we were able to obtain the isomeric 3- or 4-substituted isoquinolinone derivatives with excellent chemoselectivity. These interesting findings led us to investigate the reaction mechanism.

To gain insight into the mechanism and chemoselectivity of the reactions above, we performed a control experiment. With acetonitrile as the solvent, a radical clock experiment was carried out with 1d under the optimal reaction conditions, resulting in the formation of 2d in 54% yield, and no cyclopropyl ring opening products were observed. This result suggested that no radical intermediates were generated during the reaction (Scheme 5).

According to the aforementioned control experiment and literature precedents, we proposed a mechanism for the formation of 4-substituted isoquinolinone derivatives, including 2a. The reaction begins by tautomerization of 1a, and PISA undergoes an electrophilic reaction with 1a' to form the iodane intermediate A. The iodane A then undergoes a proton shift to provide intermediate B. Intermediate B collapses via reductive elimi-
ation to give nitrenium ion C, along with the release of iodo-benzene and sulfamate. Finally, nucleophilic attack of the olefin moiety of C on the electrophilic nitrogen atom, followed by the deprotonation with sulfamate, gives the 4-substituted isoquinolinone derivative 2a (Scheme 6).

Looking into the formation of 2c' from 1c (Scheme 2), two other resonance structures for the initially formed intermediate 1CC, namely 1CC' and 1CC'', are shown in Scheme 7. The oxygen atom in the amide motif of the substrate 1e may act as an electrophilic center, forming a C–O bond with the alkenyl group to give the isochromen-1-one oxime product 2e'.

When wet HFIP was used as the solvent, the reaction followed a different pathway. HFIP, a strong hydrogen bonding donor [26-28], interacts with the amide moiety of the substrate, and thus preventing the possible interaction between the amide moiety and PISA, as opposed to CH₃CN. The olefin moiety of the complex then interacts with the exposed central iodine(III) atom in PISA [25], forming the intermediate D. Similar cyclic iodonium intermediates were also postulated for the synthesis of
benzofuran derivatives from styrene derivatives by iodane reagents [29,30]. Subsequently, intermediate D is attacked by H$_2$O at the benzylic carbon atom to afford intermediate E. Intramolecular proton shift occurs, generating the intermediate F, which undergoes phenyl migration and reductive elimination, along with the release of iodobenzene and sulfamic acid. Cyclization of protonated G takes place to afford the intermediate H. Finally, release of water and β-proton elimination produces the rearranged product 3a (Scheme 8).

**Conclusion**

In summary, we reported the efficient synthesis of isoquinoline derivatives using a PISA-mediated methodology that chemoselectively yielded 3- or 4-substituted isoquinolinone derivatives by simply adjusting the solvent. When acetonitrile was used, the 4-substituted isoquinolinone derivatives were the reaction products, whereas hexafluoro-2-propanol led to 3-substituted isoquinolines. The solvent-dependent chemoselective synthesis of isoquinolinone derivatives is interesting and unprecedented. Further research on synthetic utility of PISA, a unique zwitterionic hypervalent iodine(III) reagent, is underway in our laboratory.

**Supporting Information**

Supporting Information File 1
Experimental details, optimization studies, compound characterization data, and spectra.
[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-20-167-S1.pdf]

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**Author Contributions**

Ze-Nan Hu: investigation; writing – original draft. Yan-Hui Wang: investigation; writing – original draft. Jia-Bing Wu: investigation. Ze Chen: investigation. Dou Hong: investigation. Chi Zhang: conceptualization; funding acquisition; project administration; resources; supervision; visualization; writing – original draft.
References