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Expeditious Synthesis of Isoquinolones and Isocoumarins with a Vinyl Borane as an Acetylene Equivalent

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Abstract

An innovative and simple expeditious synthesis of 3,4-unsubstituted isoquinolones and isocoumarins starting from safe and easy to handle two-carbon acetylene equivalent was developed. The synthetic potential of this new method was further demonstrated in the facile total synthesis of two naturally occurring alkaloids: *corydaldine* and *doryanine*.

Keywords

isoquinolone; isocoumarin; boronate; vinyl ether; Suzuki coupling

Introduction

The isoquinolone ring system is an interesting structural motif not only because of its presence in several natural compounds, but also because it is a useful building block in medicinal and organic chemistry.¹ Furthermore, its framework has been found to be a useful chemical scaffold for the synthesis of more elaborate molecules with pharmacologic properties.² Several methods have been described for the synthesis of isoquinolone building blocks.^{1c} Among them, cyclization of the corresponding o-methylbenzamide has been the most common approach; either by lithiation and reaction with dimethylformamide (DMF) or by condensation with dimethylformamide-dimethyl acetal and further cyclization using a strong base.³ Recently, a very elegant synthesis of isoquinolones from alkynes and benzamides using metal catalyzed C-H activation has also been reported.⁴ However, none of these methods is of sufficiently general applicability, especially for the synthesis of 3,4-unsubstituted isoquinolones that would require the need to use the unstable and explosive gas acetylene. Alternatively, Marsden *et al.* recently reported a method that uses a vinyl ester as an acetylene equivalent (Scheme 1). However, a mixture of isoquinolones regioisomers was observed with some substrates in this approach.⁵

Like isoquinolones, isocoumarins are also found in numerous natural products and are highly valuable compounds in drug discovery.⁶ Despite the fact that many methods to

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synthesize isocoumarins have been reported,⁷ the metal catalyzed C–H functionalization has recently emerged as the most useful and environmentally friendly method thus far.⁸ Unfortunately, these methods often lack regio- and chemoselectivity. Moreover, none of these approaches is sufficiently suitable for the synthesis of 3,4-unsubstituted isocoumarins. Notably, vinyl acetate has been recently used as an acetylene equivalent in the C–H activation/annulation to form 3,4-unsubstituted isocoumarins.⁹ However, only one example in low yield was reported.

To circumvent this problems, we hypothesized that the simple vinyl boronate **4**¹⁰ can behave as a safe and easy to handle two-carbon acetylene equivalent to facilitate the synthesis of 3,4-unsubstituted isoquinolones as well as isocoumarins (Scheme 1). Herein, we introduce a new synthetic approach under mild conditions using a vinyl ether intermediate, which can be hydrolyzed in-situ to give the cyclic isoquinolone in a one step process. Additionally, we demonstrated the versatility of this process by applying the same approach to the synthesis 3,4-unsubstituted isocoumarins. Thus, starting from the *o*-bromoaryl esters the corresponding isocoumarins are obtained in high yields.¹¹

In an effort to develop a novel and straightforward method to access isoquinolones, we hypothesized and quickly reduced to practice the idea that the commercially available boronic ester **4** can be coupled with bromoaryl carboxamides via a Suzuki reaction under very mild condition providing the corresponding vinyl ether. This enol-ether can be hydrolyzed in-situ to the corresponding aldehyde intermediate, which should react spontaneously with the carboxamide moiety to give the cyclic isoquinolone product under acidic condition (Scheme 2).

Results and Discussion

Initial experiments established the feasibility of the proposed sequence and provided insights into the robustness of the method. First, the *o*-bromoaryl carboxamide **1a** was reacted with **4** under standard Suzuki coupling conditions to afford **2a** in excellent yield.¹² The aryl carboxamide vinyl ether **2a** was then refluxed in TFA for 16 h.¹³ Gratifyingly, the desired product **3a** was isolated in 77% yield after silica gel purification. However, long reaction times were required to achieve this transformation. Therefore, to expedite the reaction, the cyclization was next carried out under microwave-assisted conditions (Table 1). When **2a** was dissolved in TFA and heated under microwave conditions at 100 °C for 2 h, product **3a** was recovered in 97% yields by a simple solvent evaporation (Table 1, entry 1). This result suggested that although microwave heating is not essential in this process, the reactions are significantly accelerated, resulting in fewer side reactions. To study the generality and scope of this methodology, **2b**, **2c**, **2d** and **2e** were synthesized and carried to the next step. The corresponding products **3b**, **3c**, **3d** and **3e** were isolated in high yield (82–93%) irrespective of the substitution in the aryl group (Table 1, entries 2–5).

Encouraged by the robustness of this synthetic approach to isoquinolones, we next attempted to apply the method to heterocyclic systems. Interestingly, heterocycles were well tolerated, with **3g** and **3h** being formed in good yields, over 90% (Table 1, entries 7, 8). However, in these examples the products were obtained as the *N*-*tert*-butyl isoquinolones. We

hypothesized that *tert*-butyl of the heterocyclic compounds maybe more difficult to cleave due to protonation of the pyridine ring. As expected, heating **3h** under microwave conditions at 150 °C for 2 h afforded **5a** in 78% yield. In this manner, **5b** was also isolated in good yield (83%) with this condition starting directly from **2g** (Scheme 3).

Based on the success of our isoquinolones synthetic method, the potential application of this approach to access isocoumarins was next investigated. We discovered that the reaction tolerated various electron-withdrawing and electron-donating groups, and that the outcome of this reaction is minimally perturbed by the substitution on the aryl ring. In all cases, the isocoumarin products were isolated in good to excellent yields from 70 to 98% (Table 2, entries 1–9). Moreover, heterocycles were also well tolerated, with **8g** and **8k** being formed in excellent yields, 98 and 96%, respectively (Table 2, entries 7 and Scheme 3).

Notably, nucleophilic aromatic substitution of the chlorine atom of **8j** by water occurred under microwave-assisted conditions leading to **8k** as the sole product (Scheme 4). structure of **8k** was confirmed by X-ray diffraction.¹⁴ To circumvent this issue, **7j** was refluxed in TFA for 16 h. Gratifyingly, **8j** was isolated in this condition in 59% yields (Table 2, entry 10) along with **8k** (11%). This finding revealed that the reactivity of **7j** can be modulated to give either **8j** or **8k** selectively.

Finally, having established a robust synthetic approach to isoquinolones and isocoumarins, an expeditious total synthesis of two naturally occurring isoquinolone alkaloids corydaldine and doryanine was explored (Scheme 5).¹⁵ The corydaldine synthesis was initiated by a Suzuki coupling between **4** and **1i** to afford **2i**, which then underwent a cyclization process to give **3i**. Subsequent platinum-catalyzed reduction of **3i** led to corydaldine **9**¹⁶ with 74% isolated overall yields in 3 steps. Thus, it represents an improved synthesis of *corydaldine* (Molander synthesis, 22% yields in 3 steps).¹⁶ **3j** was also synthesized and reacted with methyl iodide, affording straightforward access to the natural alkaloid doryanine **10**¹⁷ in good yield, 63% in 3 steps. This approach gave also better overall yield than Argade¹⁷ doryanine synthesis (63% and 55% yields respectively).

Conclusions

In conclusion, we have successfully developed a facile method for the synthesis of 3,4-unsubstituted isoquinolones and isocoumarins starting from simple substrates. The keystone of this method is the use of a vinyl boronate which behaves as a safe and easy to handle two-carbon acetylene equivalent. This approach is regioselective, highly efficient and tolerant of a broad range of aromatic substituents. This method is a valuable alternative to those substitution patterns not available through the C-H activation/condensation route. The synthetic utility of the method was further highlighted by the efficient total synthesis of two natural products: corydaldine and doryanine.

Experimental Section

General comments

Unless otherwise indicated, common reagents or materials were obtained from commercial source and used without further purification. Tetrahydrofuran (THF) and Dichloromethane (CH_2Cl_2) was dried by a PureSolvTM solvent drying system. Flash column chromatography was performed using silica gel 60 (230–400 mesh). Analytical thin layer chromatography (TLC) was carried out on Merck silica gel plates with QF-254 indicator and visualized by UV or KMnO_4 . ^1H and ^{13}C NMR spectra were recorded on an Agilent DD₂ 500 (500 MHz ^1H ; 125 MHz ^{13}C) or Agilent DD₂ 600 (600 MHz ^1H ; 150 MHz ^{13}C) or Agilent DD₂ 400 (400 MHz ^1H ; 100 MHz ^{13}C) spectrometer at room temperature. Chemical shifts were reported in ppm relative to the residual CDCl_3 (δ 7.26 ppm ^1H ; δ 77.00 ppm ^{13}C), CD_3OD (δ 3.31 ppm ^1H ; δ 49.00 ppm ^{13}C), or d_6 -DMSO (δ 2.50 ppm ^1H ; δ 39.52 ppm ^{13}C). NMR chemical shifts were expressed in ppm relative to internal solvent peaks, and coupling constants were measured in Hz. (bs = broad signal). ^{19}F NMR chemical shifts were determined relative to CFCl_3 as an internal standard (δ 0.0 ppm). High-resolution mass spectra (HRMS) were obtained using electrospray ionization (ESI) on a time of flight (TOF) mass spectrometer. All microwave reactions were conducted in sealed reaction vessels (2–5 mL) using a Biotage Initiator+ microwave reactor operating at the normal absorption level. The reaction temperatures were measured using IR. Reaction times refer to the hold time at the desired set temperature.

General Procedure for Synthesis of 2a–j

To a solution of bromo-*N*-*tert*-butyl-benzamide (0.91 mmol) in Dioxane (21 mL) in a schlenk tube was added K_2CO_3 (2.74 mmol) and water (2.00 mL). The reaction mixture was degassed by three vacuum/argon cycles at room temperature. Then Tricyclohexylphosphine (0.09 mmol), $\text{Pd}(\text{dba})_2$ (0.05 mmol) and 2-[(*E*)-2-ethoxyvinyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.91 mmol) were added into under argon. The reaction was heated with vigorous stirring at 80 °C and stirred for 2 h. It was then allowed to cool to room temperature and the mixture poured onto an aqueous saturated solution of NaCl (30 mL). The product was extracted with EtOAc (2×30 mL). EtOAc layers were combined, dried (Na_2SO_4) and concentrated in vacuo. The crude material was diluted in CH_2Cl_2 (2 mL) and purified using flash chromatography with the eluent specified in the SI.

General Procedure for Synthesis of 3a–j

A solution of *N*-*tert*-butyl-2-[(*E*)-2-ethoxyvinyl]-benzamide (0.26 mmol) in TFA (2 mL) in a sealed microwave reactor vial was heated at 100 °C for 2 h under microwave assisted conditions. The reaction mixture was evaporated to dryness. The residue was diluted in CH_2Cl_2 (2 mL) and purified using flash chromatography with the eluent specified in the SI.

General Procedure for Synthesis of 7a–j

The same procedure as that for **2** was used to synthesize **7a–j** using the corresponding starting materials.

General Procedure for Synthesis of 8a–k

The same procedure as that for **3** was used to synthesize **8a–k** using the corresponding starting materials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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1) previous work

2) This work

Scheme 1.
Approaches to 3,4-unsubstituted isoquinolones.

Scheme 2.

Our approach to 3,4-unsubstituted isoquinolones and isocoumarin.

Scheme 3.
Modified reaction conditions.

Scheme 4.
Synthesis of **8k**.

Scheme 5. Synthesis of corydaldine **9** and doryanine **10** using this method.

Table 1

Substrate scope of the isoquinolones synthesis.

		2		3	
entry	R	Yield[c]	Yield[c]	Yield[c]	Yield[c]
1	5-F	1a	2a 90%	3a	97%
2	-H	1b	2b 94%	3b	93%
3	4-CF ₃	1c	2c 76%	3c	92%
4	4-Cl	1d	2d 44%	3d	82%
5	5-OMe	1e	2e 45%	3e	89%
6		1f	2f 92%	3f	91%
7		1g	2g 71%	3g *	91%
8		1h	2h 53 %	3h *	90%

[a] Conditions: o-bromoaryl carboxamide (0.91 mmol), PCy₃ (0.09 mmol), Bis(dba)Pd⁰ (0.05 mmol), K₂CO₃ (2.74 mmol) and **4** (0.91 mmol) in THF (21 mL) / water (2.5 mL) for 2 h at 80 °C.

[b] Conditions: aryl carboxamide vinyl ether (0.26 mmol) in TFA (2 mL) for 2 h at 100 °C (μW).

^{c)} Isolated yields after chromatography.
* The *N-tert-butyl* product was isolated in this case.

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Table 2

Substrate scope of the isocoumarins synthesis.

entry	R	7	Yield ^[b]	8	Yield ^[a]
1	5-F	6a	7a	8a	82%
2	-H	6b	7b	8b	93%
3	4-CF ₃	6c	7c	8c	92%
4	4-Cl	6d	7d	8d	70%
5	5-OMe	6e	7e	8e	84%
6		6f	7f	8f	93%
7		6g	7g	8g	98%
8	4-F	6h	7h	8h	95%
9	4,5-OMe	6i	7i	8i	97%
10		6j	7j	8j	59%*

^[a] Conditions as under table 1 but using *o*-bromoaryl ester and the corresponding *o*-bromoaryl vinyl ester.^[b] Isolated yields after chromatography.

* This reaction was performed at reflux temperature for 16 h.

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