


 Cite this: *RSC Adv.*, 2020, 10, 9934

 Received 24th January 2020
 Accepted 2nd March 2020

DOI: 10.1039/d0ra00768d

rsc.li/rsc-advances

Rapid synthesis of 3-amino-1*H*-isochromene from *ortho*-ynamidyl het(aryl) aldehyde derivatives†

 Loïc Habert, Iryna Diachenko  and Isabelle Gillaizeau *

A simple and original efficient synthesis of 3-amino-1*H*-isochromene bearing a bromine atom at the C-1 position *via* a 6-endo-cyclization approach from *in situ* generated *ortho*-ynamidyl het(aryl) aldehyde derivatives is achieved under mild reaction conditions and with good yields. Original *ortho*-ynamidyl benzaldehyde compounds were also successfully obtained.

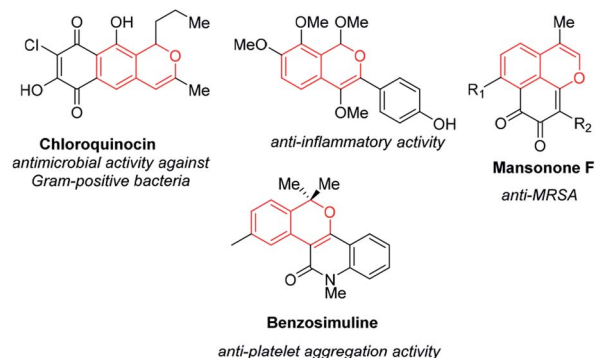
Introduction

Efficient efforts have been devoted toward developing methods and technologies to synthesize original collections of small heterocyclic molecules with useful therapeutic properties. Due to its potent biological activities, the 1*H*-isochromene framework has attracted considerable attention. A significant number of functionalized 1*H*-isochromene derivatives have been reported to have significant biological activities including antimicrobial¹ and antifungal activity,² and some exhibit a dual antiproliferative and anti-MRSA effect³ (Scheme 1). Several methods have been developed for the synthesis of this 1*H*-isochromene scaffold. Most of them involved either a transition metal-catalyzed (*i.e.* Au, Pd, Ag, Ru and Cu) annulation of 2-alkynyl benzaldehyde derivatives with alcohols⁴ or an electrophilic iodocyclization approach.⁵ Achieving the cyclization process in presence of *C*-, *O*-, or *P*-nucleophiles permitted the introduction of various substituents at the C-1 position of 1*H*-isochromene. However, most of these examples illustrate the difficulty of predicting the regioselectivity of the 5-*exo*- vs. 6-*endo*-dig ring closure depending on the nature of the starting derivatives. It should be mentioned that Walsh and Yang recently solved this regioselectivity issue using a cascade radical cyclization strategy from a 2-aza allyl anion.⁶ The literature survey thus clearly pointed out the lack of simple, cost-effective, atom-economic and fast protocols for accessing these useful frameworks. In view of our previous reports devoted to the functionalization of ynamide to provide key intermediates in the synthesis of small nitrogen-containing scaffolds,^{7,8} we anticipated benefiting from the high reactivity of these derivatives to access original functionalized 3-amino-1*H*-isochromene derivatives. This achievement will constitute a breakthrough in this field. To the best of our knowledge, there are indeed only

two reported syntheses of 3-amino-1*H*-isochromene derivatives observed as a side compound.⁹ Pursuing this objective and considering our previous reports in ynamide chemistry,⁷ we wish therefore to report herein our preliminary results on the unprecedented synthesis of functionalized 3-amino-1*H*-isochromene compounds from *ortho*-ynamidyl het(aryl) aldehyde derivatives in metal-free conditions.

Results and discussion

Access to the brominated precursor **2a–e** was achieved from readily available 2-ethynylbenzaldehydes **1a–e** according to the bromination method described by Jin's team (Table 1).¹⁰ We started our investigation by combining 2-ethynylbenzaldehyde **1a** with NBS as a brominating agent and DBU as a base in acetonitrile.¹¹ Under these conditions, a good conversion of **1a** was attained in less than one minute leading to the brominated 2-ethynylbenzaldehyde **2a** in excellent yield. Then, we investigated the influence of the aryl substitution pattern and found that the presence of a strong 3-OMe electron-donating group leads to product **2b** with good yield, whereas a 4-CH₃ group (**2c**) triggered a significant reduction in the yield, as did the presence of a 4-F electron-withdrawing group (**2d**). Good yield was also



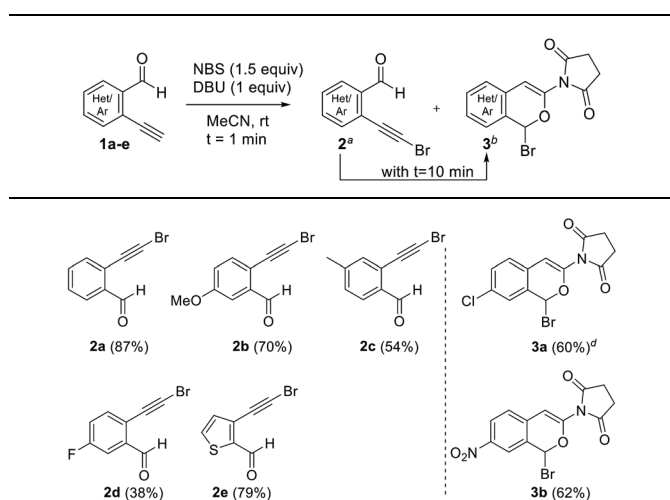
Scheme 1 Biologically active 1*H*-isochromene derivatives.

Institute of Organic and Analytical Chemistry, ICOA, UMR 7311, CNRS, Université d'Orléans, rue de Chartres, 45100 Orléans, France. E-mail: isabelle.gillaizeau@univ-orleans.fr

† Electronic supplementary information (ESI) available: Detailed experimental procedure and analytical data. See DOI: 10.1039/d0ra00768d



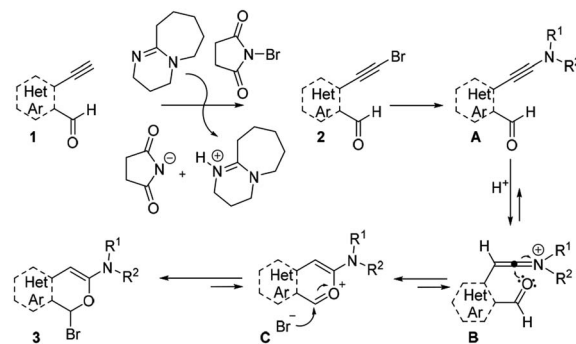
Table 1 Scope of the addition/cycloisomerization reaction from 2-ethynylbenzaldehydes 1^a



^a Reaction conditions: **1** (1 mmol), NBS (1.5 equiv.), DBU (1 equiv.), CH₃CN (2.0 mL), rt, 1 min. ^b Reaction conditions: **1** (1 mmol), NBS (1.5 equiv.), DBU (1 equiv.), CH₃CN (2.0 mL), rt, 10 min. ^c Isolated yields. ^d Gram scale synthesis.

obtained with a thiophene group allowing access to the heterocyclic product **2e**. It is important to note that the reaction time plays a key role in the formation of the targeted product. As the bromination reaction is very fast, **2** was obtained in only one minute. However, when the reaction was stirred for a longer period of time (10 minutes), we found that a new cyclized product **3a** or **3b** appeared as a unique compound when electron-withdrawing groups (*i.e.* Cl, NO₂) were present on the aryl moiety. The scalability of the cyclization was then explored by conducting the reaction at gram-scale, leading to **3a** in good yield. It is worth noting, however, that the compounds **3** were found to be unstable over time even at low temperature. Traditional functionalization by a cross-coupling reaction can thus be envisaged from **3a**, which can be furthermore considered as an oxocarbenium ion precursor. The replacement of NBS with *N*-bromophthalimide in order to increase the diversity on the imide moiety was unfortunately not successful.¹²

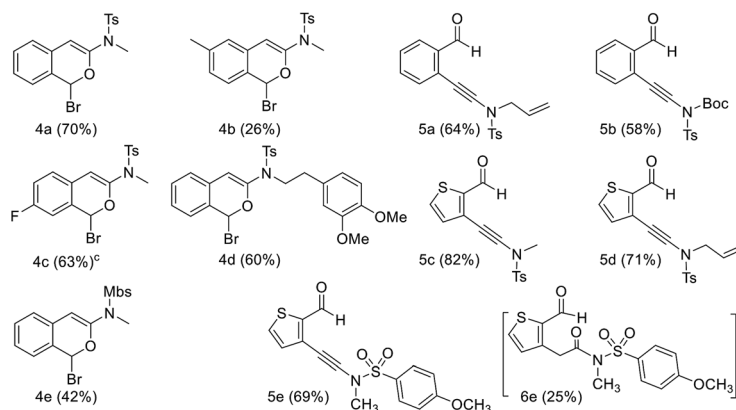
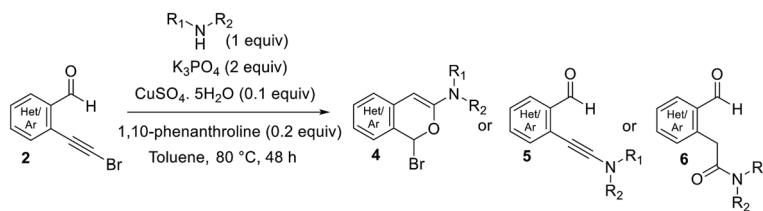
Intrigued by the formation of the cyclized product **3**, and based on the literature precedents, a plausible mechanism is outlined in Scheme 2. We initially assumed the formation of the brominated 2-ethynylbenzaldehyde **2** *via* a bromination reaction accomplished in presence of DBU and NBS. Then, the deprotonated form of succinimide attacks the brominated product **2** according to a nucleophilic substitution¹³ reaction leading to the 2-ynimidybenzaldehyde **A**, which was not isolated at this stage. It should be noted that ynimides are difficult to access; only two groups have described their synthesis in the literature to date.¹⁴ In addition, the formation of 2-ynimidybenzaldehyde is totally unprecedented, unlike the corresponding ester compound.¹⁵ This process then allows the release of hydrogen bromide in the medium which can then react with the newly formed ynimide **A**, affording the keteniminium **B** and promoting a regioselective 6-endo-dig



Scheme 2 Plausible mechanism.

intramolecular nucleophilic attack of carbonyl oxygen to the isobenzopyrylium intermediate **C**. Nucleophilic addition of the bromide anion on the latter provides access to the 3-amino-1*H*-isochromene **3**.

Taking into account this reactivity, we set about extending this methodology by modifying the nature of the amino substituent (Table 2). With a view to obtaining various 3-amino-1*H*-isochromene motifs **4**, we first attempted from **2** to replace the imide (NBS), as described in **3**, by a tosylamide in presence of DBU, but without success. Thus, to generate the precursor of the cyclization process (similar to **A** in Scheme 2), the Hsung coupling strategy was chosen for the synthesis of the 2-ynamidybenzaldehyde intermediate.⁷ A study was then carried out by varying the nature of the amide or aryl group.¹⁶ Reported reaction conditions were used from **2** without any modification affording **4a** in good yield. As previously observed in Scheme 2, lower yields were observed with electron-donating groups (**4b**) as competing substrate decomposition was observed prior to the complete consumption of the starting material. In this case, we assume that an electron-donating group (*i.e.* 4-Me) may favor the reverse addition step (*cf.* Scheme 2, intermediate **B**), causing degradation.¹⁷ The presence of electron-withdrawing groups such as fluorine (**4c**) made the final cyclized compound more stable but slowed down the cyclization process ($t = 54$ h). In a second step, variation of the amide protecting group was studied, demonstrating the possibility to access compounds **4d-e**. However, the introduction of an allyl or a Boc group on the nitrogen atom led to the formation of the corresponding 2-ynamidybenzaldehyde **5a** or **5b** in moderate yield; no cyclization product was obtained. The tests carried out using this intermediate **5** to force the cyclization reaction in neutral or acidic conditions proved unsuccessful, only degradation products were observed. Hence, given the prevalence of heterocycles in medicinal chemistry, we then tested the possibility of increasing the level of structural complexity by introducing a thiophene moiety (**5c-e**). However, no cyclization was observed either; these original thiophenyl ynamides **5c-e** were isolated as stable compounds. In the case of **5e**, the corresponding amide **6e**, resulting from a hydration process, was isolated as a side compound. Remarkably, it is the first reported example of isolated *ortho*-ynamidyl het(aryl) aldehyde derivatives and thus provides access to more complex compounds, thereby allowing the exploration of a new chemical space in

Table 2 Synthesis of 3-amino-1-bromo-1*H*-isochromene motifs **4** or *ortho*-ynamidyl het(aryl) aldehyde **5**^{ab}

^a Reaction conditions: **2** (1.1 mmol, 1.1 equiv.), R₁R₂NH (1 equiv.), K₃PO₄ (2 equiv.), CuSO₄·5H₂O (0.1 equiv.), 1,10-phenanthroline (0.2 equiv.), toluene (0.33 M), 80 °C, 48 h. ^b Isolated yields. ^c *t* = 54 h.

terms of heteroatom-containing compounds. Finally, we presumed that the electronic nature of the het(aryl) moiety directly impacted the reactivity of the aldehyde function. This trend was confirmed with electron-rich thiophene-2-carboxaldehyde derivatives (**5c–e**) which did not undergo cyclization probably due to a lower stability of the potential isobenzopyrylium intermediate **C**. Similar results were observed with the less stabilized ynamides **5a–b**.

Conclusions

In summary, the strategy developed herein is likely to provide an original and convenient access to 3-amino-1-bromo-1*H*-isochromene from readily available 2-ethynylbenzaldehydes as starting materials. The approach involved an unprecedented 2-ynamidylbenzaldehyde intermediate, which can be isolated as a stable compound. A tandem addition/cycloisomerization reaction provided regioselective access to 3-amino-1*H*-isochromene bearing a bromine atom at the C-1 position that would otherwise be difficult to prepare using alternative procedures. The use and application of the reported protocols in the synthesis of biologically important related molecules may be anticipated and is the focus of ongoing research.

Experimental

General information

Unless otherwise noted, all reagents and solvents were purchased from commercial sources and used as received. All

manipulations were conducted under argon. The reactions were monitored by thin-layer chromatography (TLC) using silica gel (60 F254) plates. Compounds were visualized using a UV lamp (254 nm) and/or by potassium permanganate stain. Flash column chromatography was carried out on silica gel 60 (230–400 mesh, 0.040–0.063 mm). Melting points (mp [°C]) were taken on samples in open capillary tubes and are uncorrected. The infrared spectra of compounds were recorded on a Thermo Scientific Nicolet iS10. ¹H, ¹³C and ¹⁹F NMR spectra were recorded on a spectrometer at 250 MHz (¹³C, 62.9 MHz) or 400 MHz (¹³C, 100 MHz; ¹⁹F: 376 MHz CPD). High-resolution accurate mass measurements (HRAM) were recorded with a Maxis Bruker 4G instrument and were performed in positive mode with an ESI source on a Q-TOF mass spectrometer with an accuracy tolerance of 2 ppm by the “Fédération de Recherche” ICOA/CBM (FR2708) platform. Compounds **1b–d**,¹⁸ **1e**¹⁹ were synthesized according to the literature procedures.

General procedure GP1 for the synthesis of **2a–2e**

To a solution of aryl alkyne **1** (1.0 mmol) in MeCN (2.0 mL) was added NBS (1.5 mmol) and DBU (1.0 mmol). The mixture was stirred at room temperature for 1 min. The reaction mixture was then poured into water and extracted with CH₂Cl₂ (3 × 10 mL). The combined organic phases were washed with water (3 × 10 mL), filtered and concentrated under reduced pressure. The crude product **2** was purified by flash-column chromatography on silica gel.

General procedure GP2 for the synthesis of 3a–3b

To a solution of aryl alkyne **1**¹⁹ (1.0 mmol) in MeCN (2.0 mL) was added NBS (1.5 mmol) and DBU (1.0 mmol). The mixture was stirred at room temperature for 10 min. The reaction mixture was then poured into water and extracted with CH₂Cl₂ (3 × 10 mL). The combined organic phases were washed with water (3 × 10 mL), filtered and concentrated under reduced pressure. The crude product **3** was purified by flash-column chromatography on silica gel.

General procedure GP3 for the synthesis of 4a–4e, 5a–5e, 6e

In a reaction vial flushed with argon and equipped with a stirring bar, were added bromoalkyne **2** (1.1 equiv.), the protected secondary amine (1.0 equiv.), CuSO₄·5H₂O (10 mol%), 1,10-phenanthroline (20 mol%), K₃PO₄ (2.0 equiv.) and toluene (0.33 M). The reaction mixture was capped and heated in an oil bath at 80 °C for 48 h while being monitored with TLC analysis. Upon completion, the reaction mixture was cooled to room temperature and diluted with EtOAc and filtered through Celite™, and the filtrate was concentrated *in vacuo*. The crude products were purified by silica gel flash column chromatography [gradient eluent: EtOAc in hexane] to afford the desired compound.

2-(Bromoethynyl)benzaldehyde (2a). Flash-column chromatography on silica gel with petroleum ether/ethyl acetate (99 : 01) as eluent gave **2a** as a white solid (691 mg, 87%) according to GP1. ¹H NMR (400 MHz, CDCl₃): 10.48 (m, 1H), 7.92 (d, *J* = 7.6 Hz, 1H), 7.59–7.53 (m, 2H), 7.49–7.45 (m, 1H). ¹³C NMR (100 MHz, CDCl₃): δ 191.1, 136.8, 133.8, 133.7, 129.0, 127.3, 126.1, 76.0, 57.2. HRMS (ESI⁺): calcd for C₉H₆OBr [M + H]⁺: 208.9596 found 208.9594. Mp: 114–115 °C.

2-(Bromoethynyl)-5-methoxybenzaldehyde (2b). Flash-column chromatography on silica gel with petroleum ether/ethyl acetate (99 : 01) as eluent gave **2b** as a white solid (298 mg, 98%) according to GP1. ¹H NMR (400 MHz, CDCl₃): 10.44 (s, 1H), 7.49 (d, *J* = 8.6 Hz, 1H), 7.39 (d, *J* = 2.8 Hz, 1H), 7.10 (dd, *J* = 8.6, 2.8 Hz, 1H), 3.86 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 191.0, 160.0, 138.3, 135.1, 121.5, 118.7, 110.0, 75.9, 55.6, 55.1. HRMS (ESI⁺): calcd for C₁₀H₈O₂Br [M + H]⁺: 238.970218 found 238.969974. Mp: 108–109 °C.

2-(Bromoethynyl)-4-methylbenzaldehyde (2c). Flash-column chromatography on silica gel with petroleum ether/ethyl acetate (99 : 01) as eluent gave **2c** as a white gum (152 mg, 54%) according to GP1. ¹H NMR (400 MHz, CDCl₃): 10.41 (d, *J* = 0.9 Hz, 1H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.39 (d, *J* = 2.1 Hz, 1H), 7.26 (s, 1H), 2.40 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 190.8, 144.9, 134.6, 134.2, 130.1, 127.4, 126.1, 76.2, 56.5, 21.5. HRMS (ESI⁺): calcd for C₁₀H₈O₂Br [M + H]⁺: 222.9753 found 222.9751.

2-(Bromoethynyl)-5-fluorobenzaldehyde (2d). Flash-column chromatography on silica gel with petroleum ether/ethyl acetate (99 : 01) as eluent gave **2d** as a white gum (233 mg, 38%) according to GP1. ¹H NMR (400 MHz, CDCl₃): 10.44 (m, 1H), 7.60–7.57 (m, 2H), 7.29–7.24 (m, 1H). ¹³C NMR (100 MHz, CDCl₃): δ 189.9, 162.5, 133.9, 135.9, 122.2, 121.3, 113.9, 75.0, 57.1. HRMS (ESI⁺): calcd for C₉H₅OFBr [M + H]⁺: 226.9502 found 226.9502.

3-(Bromoethynyl)thiophene-2-carbaldehyde (2e). Flash-column chromatography on silica gel with petroleum ether/ethyl acetate (99 : 01) as eluent gave **2e** as a white solid (1.51 g, 79%) according to GP1. ¹H NMR (400 MHz, CDCl₃): 10.11 (d, *J* = 1.3 Hz, 1H), 7.66 (d, *J* = 5.0, 1.3 Hz, 1H), 7.19 (d, *J* = 5.0 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃): δ 182.5, 145.3, 133.8, 131.8, 129.8, 72.8, 57.6. HRMS (ESI⁺): calcd for C₇H₄SOBr [M + H]⁺: 214.916074 found 214.915654. Mp: 65–66 °C.

1-(1-Bromo-7-chloro-1*H*-isochromen-3-yl)pyrrolidine-2,5-dione (3a). Flash-column chromatography on silica gel with petroleum ether/ethyl acetate (80 : 20) as eluent gave **3a** as a white solid (950 mg, 60%) according to GP2. ¹H NMR (400 MHz, CDCl₃): 7.39 (d, *J* = 1.2 Hz, 2H), 7.21 (m, 1H), 7.13 (s, 1H), 5.79 (s, 1H), 2.77–2.75 (s, 4H). ¹³C NMR (100 MHz, CDCl₃): δ 175.0, 155.3, 135.6, 132.0, 130.3, 122.0, 120.9, 82.5, 76.1, 28.1. HRMS (ESI⁺): calcd for C₁₃H₉BrClO₃N [M + Na]⁺: 363.9346 found 363.9335. Mp: 95 °C.

1-(1-Bromo-7-nitro-1*H*-isochromen-3-yl)pyrrolidine-2,5-dione (3b). Flash-column chromatography on silica gel with petroleum ether/ethyl acetate (80 : 20) as eluent gave **3b** as a white gum (240 mg, 62%) according to GP2. ¹H NMR (250 MHz, DMSO): 8.44 (s, 1H), 8.35 (dd, *J* = 8.5, 1.8 Hz, 1H), 8.00 (d, *J* = 8.5 Hz, 1H), 7.22 (s, 1H), 6.68 (s, 1H), 2.69 (d, *J* = 5.8 Hz, 4H). ¹³C NMR (63 MHz, DMSO) δ 176.8 (2 × C), 154.9, 148.5, 138.9, 138.7, 125.7, 121.7, 119.4, 82.6, 80.3, 28.7 (2 × C). HRMS (ESI⁺): calcd for C₁₃H₁₀BrO₅N₂S [M + H]⁺: 352.9768 found 352.9764.

***N*-(1-Bromo-1*H*-isochromen-3-yl)-*N*,4-dimethylbenzenesulfonamide (4a).** Flash-column chromatography on silica gel with petroleum ether/ethyl acetate (90 : 10) as eluent gave **4a** as a white solid (297 mg, 70%) according to GP3. ¹H NMR (400 MHz, CDCl₃): 7.95 (d, *J* = 8.2 Hz, 2H), 7.45–7.35 (m, 7H), 5.62 (s, 1H), 2.45 (s, 3H), 2.30 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 155.3, 143.9, 136.5, 134.6, 132.9, 130.2, 130.1, 129.6, 128.5, 123.4, 120, 92.3, 74.8, 28.1, 21.6. HRMS (ESI⁺): calcd for C₁₇H₁₇BrSO₃N [M + H]⁺: 394.0107 found 394.0105. Mp: 114–115 °C.

***N*-(1-Bromo-6-methyl-1*H*-isochromen-3-yl)-*N*,4-dimethylbenzenesulfonamide (4b).** Flash-column chromatography on silica gel with petroleum ether/ethyl acetate (99 : 01) as eluent gave **4b** as a white solid (65 mg, 26%) according to GP3. ¹H NMR (400 MHz, CDCl₃): 7.95 (d, *J* = 8.3 Hz, 2H), 7.40–7.23 (m, 5H), 7.19 (s, 1H), 5.58 (s, 1H), 2.45 (s, 3H), 2.41 (s, 3H), 2.30 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 155.3, 143.8, 140.5, 134.8, 133.9, 133.1, 131.2, 129.5, 128.4, 123.0, 120.1, 92.1, 74.3, 28.0, 21.6, 21.4. HRMS (ESI⁺): fast degradation of compound.

***N*-(1-Bromo-7-fluoro-1*H*-isochromen-3-yl)-*N*,4-dimethylbenzenesulfonamide (4c).** Flash-column chromatography on silica gel with petroleum ether/ethyl acetate (90 : 10) as eluent gave **4c** as a white solid (246 mg, 63%) according to GP3. ¹H NMR (400 MHz, CDCl₃): 7.93 (d, *J* = 8.3 Hz, 2H), 7.40–7.34 (m, 3H), 7.32 (s, 1H), 7.18–7.11 (m, 2H), 5.57 (s, 1H), 2.46 (s, 3H), 2.33 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 163.8, 154.4, 144.1, 138.8, 134.4, 129.7, 128.9, 128.4, 121.7, 118.3, 110.5, 91.7, 74.4, 28.1, 21.6. HRMS (ESI⁺): calcd for C₁₇H₁₆BrFSO₃N [M + H]⁺: 412.0012 found 412.0012. Mp: 157–158 °C.

***N*-(1-Bromo-1*H*-isochromen-3-yl)-*N*-(2-(3,4-dimethoxyphenyl)ethyl)-4-methylbenzenesulfonamide (4d).**

Flash-column chromatography on silica gel with petroleum ether/ethyl acetate (90 : 10) as eluent gave **4d** as a yellow oil (241 mg, 60%) according to GP3. ^1H NMR (400 MHz, CDCl_3): 7.96 (d, $J = 8.4$ Hz, 2H), 7.42–7.39 (m, 2H), 7.35–7.31 (m, 4H), 6.60 (d, $J = 8.1$ Hz, 1H), 6.25 (dd, $J = 8.1, 1.9$ Hz, 1H), 6.13 (d, $J = 2.0$ Hz, 1H), 5.65 (s, 1H), 3.75 (s, 3H), 3.67 (s, 3H), 2.86–2.67 (m, 3H), 2.41 (s, 3H), 2.38–2.29 (s, 1H). ^{13}C NMR (100 MHz, CDCl_3): all carbons were not visible on the NMR spectrum and the compound showed fast degradation in the NMR solvent over time. HRMS (ESI+): calcd for $\text{C}_{26}\text{H}_{27}\text{BrSO}_5\text{N}$ [$\text{M} + \text{H}$] $^+$: 544.0787 found 544.078563.

N-(1-Bromo-1H-isochromen-3-yl)-4-methoxy-N-methylbenzenesulfonamide (4e). Flash-column chromatography on silica gel with petroleum ether/ethyl acetate (90 : 10) as eluent gave **4e** as a white gum (184 mg, 42%) according to GP3. ^1H NMR (400 MHz, CDCl_3): 8.02 (d, $J = 9.0$ Hz, 2H), 7.48–7.41 (m, 4H), 7.37 (s, 1H), 7.06 (d, $J = 9.0$ Hz, 2H), 5.64 (s, 1H), 3.91 (s, 2H), 2.32 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 163.3, 155.3, 136.5, 132.9, 130.7, 130.2, 130.1, 129.1, 123.4, 119.9, 114.2, 92.4, 74.7, 55.6, 28.1. HRMS (ESI+): calcd for $\text{C}_{17}\text{H}_{16}\text{BrFSO}_3\text{N}$ [$\text{M} + \text{H}$] $^+$: 410.0056 found 410.0055.

N-Allyl-N-(2-formylphenyl)ethynyl-4-methylbenzenesulfonamide (5a). Flash-column chromatography on silica gel with petroleum ether/ethyl acetate (80 : 20) as eluent afforded **5a** as a pale yellow oil (239 mg, 64% according to GP3). ^1H NMR (250 MHz, CDCl_3): 9.88 (s, 1H), 7.95 (d, $J = 8.4$ Hz, 2H), 7.90 (d, $J = 8.5$ Hz, 1H), 7.79–7.75 (m, 1H), 7.53 (ddd, $J = 6.6, 5.3, 1.7$ Hz, 2H), 7.37 (d, $J = 8.0$ Hz, 2H), 7.24–7.19 (m, 1H), 6.07–5.86 (m, 1H), 5.40–5.21 (m, 2H), 4.53 (dt, $J = 5.6, 1.4$ Hz, 2H), 2.46 (s, 3H). ^{13}C NMR (63 MHz, CDCl_3) δ 193.1, 144.7, 136.6, 135.4, 135.1, 134.2, 133.7, 132.8, 132.6, 129.7 (2 \times C), 128.1 (2 \times C), 128.0, 118.3, 87.8, 80.1, 48.9, 21.6. HRMS (ESI+): calcd for $\text{C}_{19}\text{H}_{18}\text{O}_3\text{NS}$ [$\text{M} + \text{H}$] $^+$: 340.1002 found 340.1000.

tert-Butyl((2-formylphenyl)ethynyl)(phenyl)carbamate (5b). Flash-column chromatography on silica gel with petroleum ether/ethyl acetate (80 : 20) as eluent afforded **5b** as a pale yellow oil (205 mg, 58% according to GP3). ^1H NMR (250 MHz, CDCl_3): 10.54 (d, $J = 0.8$ Hz, 1H), 7.96–7.89 (m, 1H), 7.60–7.50 (m, 4H), 7.49–7.44 (m, 2H), 7.37–7.32 (m, 1H), 7.09–7.00 (m, 1H), 1.62 (s, 9H). ^{13}C NMR (63 MHz, CDCl_3) δ 192.0, 152.5, 139.1, 135.0, 133.7, 131.8, 129.0 (2 \times C), 128.9, 127.4, 127.1, 124.8 (2 \times C), 118.5, 90.8, 84.3, 67.1, 28.3, 28.1, 27.9. HRMS (ESI+): calcd for $\text{C}_{20}\text{H}_{20}\text{O}_3\text{N}$ [$\text{M} + \text{H}$] $^+$: 322.1438 found 322.1439.

N-(2-Formylthiophen-3-yl)ethynyl-N,4-dimethylbenzenesulfonamide (5c). Flash-column chromatography on silica gel with petroleum ether/ethyl acetate (90 : 10) as eluent gave **5c** as a yellow oil (310 mg, 82%) according to GP3. ^1H NMR (400 MHz, CDCl_3): 9.94 (d, $J = 1.3$ Hz, 1H), 7.81–7.80 (m, 1H), 7.78–7.77 (m, 1H), 7.61 (dd, $J = 5.0, 1.3$ Hz, 1H), 7.36 (dd, $J = 8.6, 0.7$ Hz, 1H), 7.06 (d, $J = 5.0$ Hz, 1H), 3.18 (s, 3H), 2.44 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 182.8, 133.9, 131.1, 130.0, 127.7, 127.4, 90.5, 63.0, 39.0, 21.7. All carbons were not visible on the NMR spectrum and the compound showed fast degradation in the NMR solvent over time. HRMS (ESI+): calcd for $\text{C}_{15}\text{H}_{14}\text{S}_2\text{O}_3\text{N}$ [$\text{M} + \text{H}$] $^+$: 320.0486 found 320.0409.

N-Allyl-N-(2-formylthiophen-3-yl)ethynyl-4-methylbenzenesulfonamide (5d). Flash-column chromatography on silica gel

with petroleum ether/ethyl acetate (90 : 10) as eluent gave **5d** as a pale yellow oil (269 mg, 71%) according to GP3. ^1H NMR (250 MHz, CDCl_3) 9.90 (s, 1H), 7.80 (d, $J = 8.4$ Hz, 2H), 7.61 (d, $J = 5.0$ Hz, 1H), 7.35 (d, $J = 8.5$ Hz, 2H), 7.05 (d, $J = 5.0$ Hz, 1H), 5.90–5.53 (m, 1H), 5.45–5.14 (m, 2H), 4.08 (d, $J = 1.2$ Hz, 2H), 2.44 (s, 3H). ^{13}C NMR (63 MHz, CDCl_3) δ 182.9, 145.3, 134, 133.9, 131.9, 131.1, 130.6, 130.0 (2 \times C), 127.7 (2 \times C), 120.7, 118.7, 84.0, 54.2, 36.4, 21.7. HRMS (ESI+): calcd for $\text{C}_{17}\text{H}_{16}\text{O}_3\text{NS}_2$ [$\text{M} + \text{H}$] $^+$: 346.0566 found 346.0565.

N-(2-Formylthiophen-3-yl)ethynyl-4-methoxy-N-methylbenzenesulfonamide (5e). Flash-column chromatography on silica gel with petroleum ether/ethyl acetate (90 : 10) as eluent gave **5e** as a colorless oil (254 mg, 69%) according to GP3. ^1H NMR (250 MHz, CDCl_3) 10.00 (d, $J = 1.2$ Hz, 1H), 7.89 (d, $J = 9.2$ Hz, 2H), 7.66 (dd, $J = 5.0, 1.4$ Hz, 1H), 7.09 (dd, $J = 8.9, 7.0$ Hz, 3H), 3.92 (s, 1H), 3.22 (s, 1H). ^{13}C NMR (63 MHz, CDCl_3) δ 182.9, 164.1, 142.4, 133.9, 131.1, 130.6, 130.0 (2 \times C), 127.6, 114.6 (2 \times C), 90.7, 63.1, 55.8, 39.0. HRMS (ESI+): calcd for $\text{C}_{14}\text{H}_{14}\text{O}_4\text{NS}_2$ [$\text{M} + \text{H}$] $^+$: 336.0359 found 336.0357.

N-(2-(2-Formylthiophen-3-yl)-2-oxoethyl)-4-methoxy-N-methylbenzenesulfonamide (6e). Flash-column chromatography on silica gel with petroleum ether/ethyl acetate (90 : 10) as eluent gave **6e** as a white gum (97 mg, 25%) according to GP3. ^1H NMR (250 MHz, CDCl_3) 9.84 (s, 1H), 7.92–7.85 (m, 2H), 7.69 (d, $J = 4.9$ Hz, 1H), 7.11–6.99 (m, 3H), 4.49 (s, 2H), 3.98–3.86 (m, 3H), 3.30 (s, 3H). ^{13}C NMR (63 MHz, CDCl_3) δ 182.3, 169.7, 163.7, 140.9, 134.0, 131.8, 130.0, 129.8, 114.6, 55.8, 36.6, 33.2. HRMS (ESI+): calcd for $\text{C}_{15}\text{H}_{16}\text{O}_5\text{NS}_2$ [$\text{M} + \text{H}$] $^+$: 355.0363 found 355.0362.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

The authors thank the LABEX SynOrg (ANR-11-LABX-0029) and the Région Centre Val-de-Loire (SynHetF) for financial support and fellowships (L. H., I. D.).

Notes and references

- H. He, H. Y. Yang, S. W. Luckman, D. M. Roll and G. T. Carter, *J. Antibiot.*, 2002, **55**, 1072.
- K. Nozawa, M. Yamada, Y. Tsuda, K. Kawai and S. Nakajima, *Chem. Pharm. Bull.*, 1981, **29**, 2689.
- G. Attardo, W. Wang, T. Breining, T. Li, Y. St-Denis and J.-L. Kraus, Int. Patent WO 9 512 588, 1995.
- (a) N. Asao, T. Nogami, K. Takahashi and Y. Yamamoto, *J. Am. Chem. Soc.*, 2002, **124**, 764; (b) N. T. Patil, H. Wu and Y. Yamamoto, *J. Org. Chem.*, 2005, **70**, 4531; (c) X. Yu, Q. Ding, W. Wang and J. Wu, *Tetrahedron Lett.*, 2008, **49**, 4390; (d) G. Mariaule, G. Newsome, P. Toullec, P. Belmont and V. Michelet, *Org. Lett.*, 2014, **16**, 4570; (e) B. Ouyang, J. Yuan, Q. Yang, Q. Ding, Y. Peng and J. Wu, *Heterocycles*, 2011, **82**, 1239; (f) X. Yao and C.-J. Li, *Org. Lett.*, 2006, **8**, 1953; (g) E. Tomás-Mendivil, J. Starck, J. C. Ortuno and

- V. Michelet, *Org. Lett.*, 2015, **17**, 6126; (h) D. Malhotra, L. -P. Liu, M. S. Mashuta and G. B. Hammond, *Chem.–Eur. J.*, 2013, **19**, 4043; (i) J. Zhao, W. Xu, X. Xie, N. Sun, X. Li and Y. Liu, *Org. Lett.*, 2018, **20**, 5461; (j) F.-H. Li, J. Li, S.-Y. Wang and S.-J. Ji, *Tetrahedron*, 2017, **73**, 5731; (k) D. Wang, S. Liu, X.-C. Lan, A. Paniagua, W.-J. Hao, G. Li, S.-J. Tu and B. Jianga, *Adv. Synth. Catal.*, 2017, **359**, 3186.
- 5 (a) J. Barluenga, H. Vázquez-Villa, A. Ballesteros and J. M. González, *J. Am. Chem. Soc.*, 2003, **125**, 9028; (b) D. Yue, N. Della Cà and R. C. Larock, *Org. Lett.*, 2004, **6**, 1581; (c) J. Barluenga, H. Vasquez-Villa, I. Merino, A. Ballesteros and J. M. Gonzalez, *Chem.–Eur. J.*, 2006, **12**, 5790; (d) A. K. Verma, T. Aggarwal, V. Rustagia and R. C. Larock, *Chem. Commun.*, 2010, **46**, 4064.
- 6 K. Yu, M. Li, G. Deng, C. Liu, J. Wang, Z. Liu, H. Zhang, X. Yang and P. J. Walsh, *Adv. Synth. Catal.*, 2019, **361**, 4354.
- 7 (a) R. Sallio, M. Corpet, L. Habert, M. Durandetti, C. Gosmini and I. Gillaizeau, *J. Org. Chem.*, 2017, **82**, 1254; (b) R. Rey-Rodriguez, G. Grelier, L. Habert, P. Retailleau, B. Darses, I. Gillaizeau and P. Dauban, *J. Org. Chem.*, 2017, **82**, 11897; (c) L. Habert, R. Sallio, M. Durandetti, C. Gosmini and I. Gillaizeau, *Eur. J. Org. Chem.*, 2019, 5175.
- 8 For recent reports on Brønsted acid or heteroatom electrophilic reagent promoted reactions of ynamides, see: (a) S. Xu, J. Liu, D. Hu and X. Bi, *Green Chem.*, 2015, **17**, 184; (b) C. Theunissen, B. Metayer, N. Henry, G. Compain, J. Marrot, A. Martin-Mingot, S. Thibaudeau and G. Evano, *J. Am. Chem. Soc.*, 2014, **136**, 12528; (c) C. Theunissen, B. Métayer, M. Lecomte, N. Henry, H.-C. Chan, G. Compain, P. Gérard, C. Bachmann, N. Mokhtari, J. Marrot, A. Martin-Mingot, S. Thibaudeau and G. Evano, *Org. Biomol. Chem.*, 2017, **15**, 4399.
- 9 (a) Y. Q. Zhang, X. Q. Zhu, Y. Xu, H. Z. Bu, J. L. Wang, T. Zhai, J. M. Zhoua and L. W. Ye, *Green Chem.*, 2019, **21**, 3023; (b) X. Chen, D. Shen, Q. Wang, Y. Yang and B. Yu, *Chem. Commun.*, 2015, **51**, 13957.
- 10 M. Li, Y. Li, B. Zhao, F. Liang and L. Y. Jin, *RSC Adv.*, 2014, **4**, 30046.
- 11 Degradation was observed using other organic and inorganic bases.
- 12 Addition of *N*-bromophthalimide and DBU to 2 did not afford compound 3.
- 13 B. Pigulski, P. Męcik, J. Cichos and S. Szafert, *J. Org. Chem.*, 2017, **82**, 1487.
- 14 (a) T. Sueda, A. Oshima and N. Teno, *Org. Lett.*, 2011, **13**, 3996; (b) J. S. Alford and H. M. L. Davies, *Org. Lett.*, 2012, **23**, 6020.
- 15 L. Habert, P. Retailleau and I. Gillaizeau, *Org. Biomol. Chem.*, 2018, **16**, 7351 and references therein.
- 16 The reaction was unsuccessful starting from the corresponding *ortho*-ynamidyl ketone derivatives.
- 17 ¹H NMR of the crude reaction mixture showed the aldehyde signal.
- 18 (a) H. Y. Wang and S. K. Tian, *Org. Lett.*, 2019, **14**, 5675; (b) Y. Ohta, Y. Kubota, T. Watabe, H. Chiba, S. Oishi, N. Fujii and H. Ohno, *J. Org. Chem.*, 2018, **15**, 7799.
- 19 (a) L. Wang, L. Liu, W. Chang and J. Li, *J. Org. Chem.*, 2018, **15**, 7799; (b) W. Debrouwer, R. Seigneur, T. Heugebaert and C. Stevens, *Chem. Commun.*, 2015, **51**, 729.