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Triflic Acid Mediated Sequential Cyclization of *ortho*-Alkynylarylesters with Ammonium Acetate

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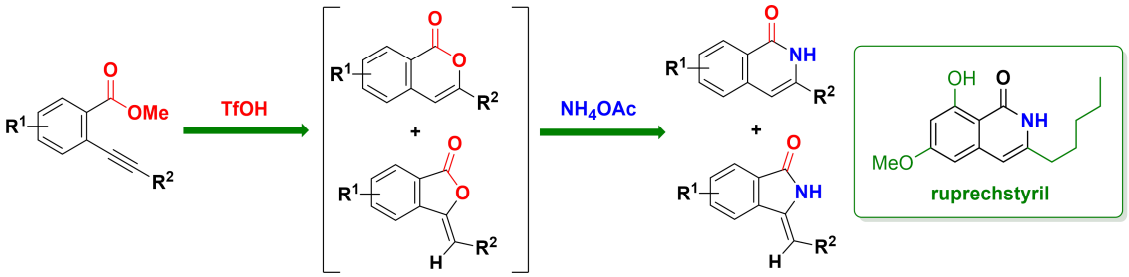

Triflic Acid Mediated Sequential Cyclization of *ortho*-Alkynylarylesters with Ammonium Acetate

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Abstract

A triflic acid (TfOH) mediated sequential cyclization of *ortho*-alkynylarylesters and ammonium acetate (NH_4OAc) was reported. The reaction took place via a Brønsted acid-mediated intramolecular cyclization of *ortho*-alkynylarylesters followed by an ammonium acetate participated substitution reaction, forming isoquinolin-1-ones as the major products. Different from most of the known synthetic methods of isoquinolin-1-ones, no metal catalyst was required in the reported reaction. The regioisomers – isoindolin-1-ones were obtained together with isoquinolin-1-ones in a few cases. The intermediate compounds – isochromen-1-ones and isobenzofuran-1-ones were also isolated. The interconversion experiments showed that the regioisomers formed during the Brønsted acid induced intramolecular cyclization of *ortho*-alkynylarylesters. A natural product – ruprechstyril was prepared in a moderate yield employing the new method.

Key words: Brønsted acid mediated, isoquinolin-1-one, isoindolin-1-one, nitrogen-containing heterocycle, ruprechstyril synthesis

Introduction

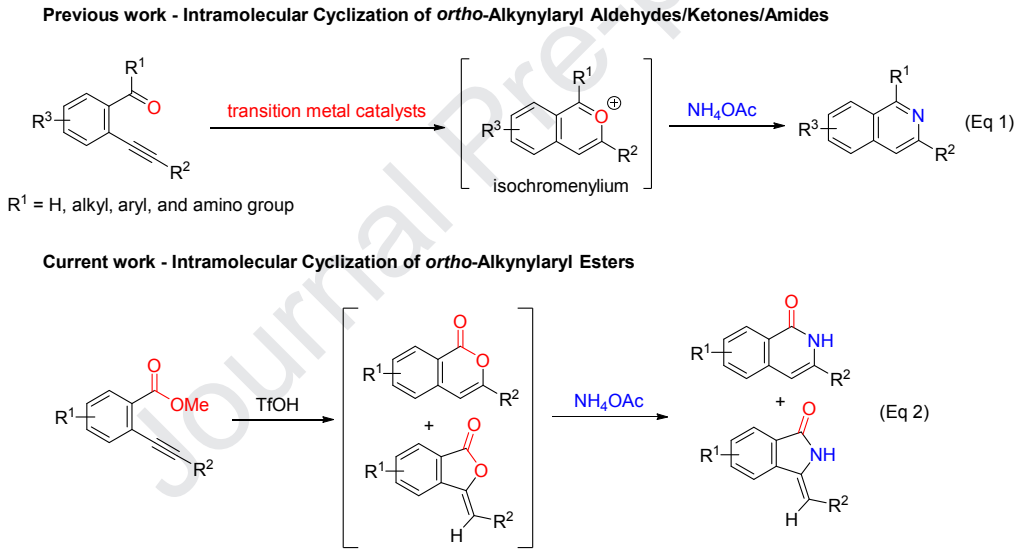
Due to the broad application in medicinal chemistry, pharmaceutical industry and material sciences, great attention has been attracted to nitrogen-containing heterocycles.[1] Among the numerous synthetic methods developed for nitrogen-containing heterocycles, the nitrogen sources employed are generally nitrogen-containing functional groups, such as amines, amides, imines, imides, azides, nitriles, isonitriles, oximes, and nitro groups.[2] The inexpensive inorganic salt, ammonium acetate, is an excellent alternative nitrogen source for its stability and readily availability. As a nitrogen source, ammonium acetate has been employed in the syntheses of quite a few of heterocycles including pyridines,[3] pyrimidines,[4] imidazoles,[5] oxazoles,[6] chromene-fused quinolinones,[7] triazoles,[8] pyrroles,[9] isothiazoles,[10] isoquinolines,[11] isoindolin-1-ones and isoquinolin-1-ones.[12]

Isoquinolin-1-ones are a group of important nitrogen-containing heterocycles for their known biological activities such as tumor growth inhibition,[13] antithrombotic efficacy,[14] and blood pressure reduction.[15] Their synthesis has attracted great interest of both medicinal and synthetic chemists.[16] The majority of the known work employed a cyclization strategy employing benzamides and alkyne substrates, including 1) transition-metal[17] or iodine reagent[18] mediated intermolecular cyclization between a directing group activated benzamides and alkynes / alkyne surrogates; 2) transition metal catalyzed intermolecular cyclization of *ortho*-halobenzamides and alkynes;[19] 3) Lewis acid mediated intramolecular cyclization of *ortho*-alkynylbenzamides.[20] Most of these methods employed nitrogen-containing organic groups such as amides or azides as the nitrogen source.

On the other hand, only in a few cases were inorganic ammonium salts employed as the nitrogen source in the isoquinolin-1-one synthesis. These included a copper-catalyzed three-component coupling of *ortho*-halobenzoic acid, alkynylcarboxylic acid and ammonium acetate[12] and a palladium-catalyzed three-component coupling of *ortho*-iodobenzoate, allene and ammonium tartrate.[21] In addition, aqueous ammonia was used in preparing the isoquinolin-1-one core structure in a total synthesis of cassiarin A[22] and ruprechstyril.[23] To our best knowledge, Brønsted acid-mediated one-pot synthesis of isoquinolin-1-one using simple inorganic ammonium salts as the nitrogen source still remains unknown.

Our group has been developing efficient synthetic methods for nitrogen-containing heterocycles using cascade/one-pot reaction protocols. We have successfully employed NH_4OAc as the nitrogen source in the synthesis of a variety of isoquinolines, by an intramolecular cyclization of *ortho*-alkynylaryl aldehydes/ketones/amides and a subsequent substitution of the oxygen atom in the isochromenylium intermediate by NH_4OAc (Eq 1, Scheme 1).[11] We have further extended the cyclization strategy to *ortho*-alkynylarylesters, and we herein report our new results on a Brønsted acid mediated one-pot reaction of *ortho*-alkynylarylesters and ammonium acetate (Eq 2, Scheme 1).

Scheme 1. Intramolecular Cyclization of *ortho*-Alkynylaryl Aldehydes/Ketones/Amides/Esters and Subsequent Ammonium Acetate Participated Substitution

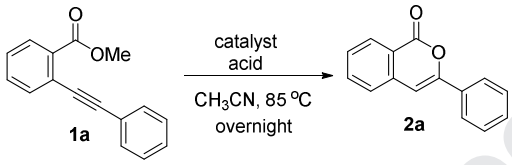


Results and discussion

We chose methyl 2-(phenylethynyl)benzoate (**1a**) as the model substrate for reaction condition optimization. After several attempts, we realized the conditions of the intramolecular cyclization of ester **1a** and the subsequent NH_4OAc participated substitution were incompatible with each other in a cascade reaction protocol. We, therefore, attempted a one-pot reaction protocol for the designed reaction, and decided to first optimize the conditions of the intramolecular cyclization of ester **1a**. The cyclization took place smoothly in the presence of $NaAuCl_4$ (10 mol%) / $AgSbF_6$ (10 mol%) and 1.1 equiv TfOH in

acetonitrile (CH_3CN) at 85 °C, affording the desired product isochromenone **2a** in 91% yield (Table 1, entry 1). Other acids such as trifluoroacetic acid (TFA) and methanesulfonic acid (MsOH) afforded much lower yields (Table 1, entries 2 and 3). In the presence of 10 mol% CuI and 1.1 equiv TfOH, **2a** was obtained in 81% yield (Table 1, entry 4). When the amount of TfOH was increased to 2.2 equiv, **2a** was obtained in 84% yield even in the absence of any transition metal catalyst (Table 1, entry 5).

Table 1. Condition Optimization for Intramolecular Cyclization of 2-(Phenylethynyl)benzoate (**1a**)[a]



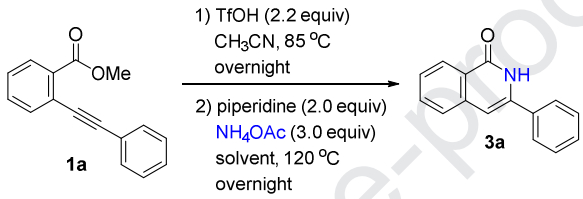
entry	catalyst (10 mol%)	acid	**2a** yield (%)[b]
1	$NaAuCl_4/AgSbF_6$	TfOH (1.1 equiv)	91
2	$NaAuCl_4/AgSbF_6$	TFA (1.1 equiv)	44
3	$NaAuCl_4/AgSbF_6$	MsOH (1.1 equiv)	42
4	CuI	TfOH (1.1 equiv)	81
5	-	TfOH (2.2 equiv)	84

[a] Representative procedure: A 20 mL glass reaction vial was charged with **1a** (2.0 mmol, 1.0 equiv), a catalyst (0.1 equiv), an acid, and acetonitrile (10 mL). The vial was then flushed with nitrogen and sealed with a pressure relief cap. The reaction mixture was stirred at 85 °C overnight. [b] Isolated yields after column chromatography.

Considering the chemical yields of **2a** and the catalyst cost, we chose the conditions listed in Entry 5 in Table 1 as the first step optimal conditions, and continued optimizing the second step. After several attempts, we found that the solvent, CH_3CN, was incompatible for both steps. Therefore, after the

completion of the first step, the reaction mixture was first neutralized by piperidine (2.0 equiv), and CH_3CN was then removed using a rotary evaporator under reduced pressure (20 mmHg). Ammonium acetate (3.0 equiv) and a new solvent, DMAc (5 mL), were then added to the reaction mixture. The resulting mixture was heated at 120 °C overnight, affording the desired isoquinolin-1-one **3a** in 75% yield (Table 2, entry 1). Other solvents such as *N*,*N*-dimethylformamide (DMF) and *N*-methylpyrrolidin-2-one (NMP) provided lower chemical yields (Table 2, entries 2-3).

Table 2. Condition Optimization for the One-Pot Reaction of 2-(Phenylethynyl)benzoate (**1a**) and Ammonium Acetate[a]



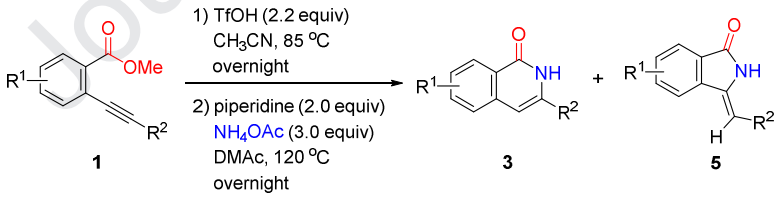
entry	solvent	**3a** yield (%)[b]
1	DMAc	75
2	DMF	65
3	NMP	65

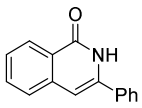
[a] Representative procedure: A 20 mL glass reaction vial was charged with **1a** (2.0 mmol, 1.0 equiv), triflic acid (660.3 mg, 4.4 mmol, 2.2 equiv) and acetonitrile (10 mL). The vial was then flushed with nitrogen and sealed with a pressure relief cap. The reaction mixture was stirred at 85 °C overnight, until the disappearance of starting material **1a** was observed. After completion, the reaction mixture was cooled to room temperature and piperidine (340.6 mg, 4.0 mmol, 2.0 equiv) was added, while stirring continued for 30 min. The solvent was evaporated using a rotary evaporator. Ammonium acetate (462.5 mg, 6.0 mmol, 3.0 equiv) and a new solvent (5 mL) were then added to the reaction mixture. The resulting reaction mixture was heated at 120 °C overnight, until the disappearance of intermediate compound **2a** was observed. [b] Isolated yields after column chromatography.

We next examined the substrate scope of the triflic acid mediated one-pot reaction of *ortho*-alkynylarylesters and ammonium acetate, using the optimal conditions listed in Entry 1 in Table 2. Although aryl, heteroaryl, alkenyl, and alkyl groups were all well accommodated at the distal end of the alkyne bond (**3a**, **3b**, **3i**, **3j**, **3k**, and **3l** in Table 3), a pair of regioisomers – isoquinolin-1-ones (**3k** and

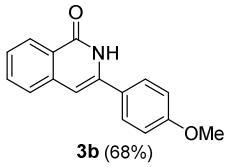
3l) and isoindolin-1-ones (**5k** and **5l**) were obtained when the distal group (R^1) was an alkyl. The steric hindrance from the distal alkyl group seemed to favor the formation of the isoindolin-1-one isomer (55% yield for **5l**, vs, 7% yield for **5k**). An interesting electronic effect on both the proximal and distal phenyl rings on the alkyne bond was also observed. Although both electron-donating and electron-withdrawing groups on these rings were tolerated in the reaction (**3b**, **3c**, **3d**, **3e**, **3f**, **3g**, and **3h**), their locations on the two phenyl rings seemed to have a significant impact on the regioselectivity of the cyclization. In general, the cyclization took place in a *6-endo-dig* mode to form isoquinolin-1-ones (**3**). But, the presence of either an electron-donating group at the *para*-position on the proximal phenyl ring (**3d**, **5d**, **3h**, and **5h**) or an electron-withdrawing group at the *para*-position on the distal phenyl ring (**3c** and **5c**) led to both *6-endo-dig* and *5-exo-dig* cyclizations forming a pair of regioisomers. The cyclization of methyl 2-((trimethylsilyl)ethynyl)benzoate (**1m**) failed under the optimized conditions listed in Entry 1 in Table 2. On the other hand, its cyclization was successful in the presence of $NaAuCl_4$ (10 mol%) / $AgSbF_6$ (10 mol%) and 1.1 equiv TfOH, affording a desilylated isoquinolin-1-one (**3m**) in a 60% yield.

Table 3. Triflic Acid Mediated One-pot Reaction of *ortho*-Alkynylarylesters and Ammonium Acetate[a]

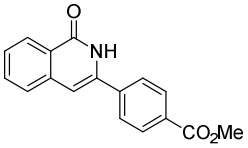




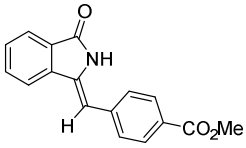
3a (75%)



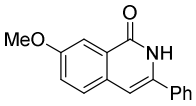
3b (68%)



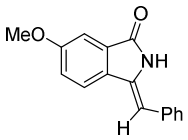
3c (51%)



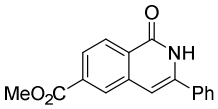
5c (15%)



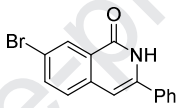
3d (15%)



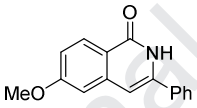
5d (46%)



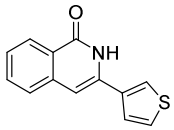
3e (66%)



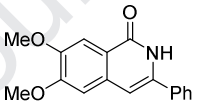
3f (72%)



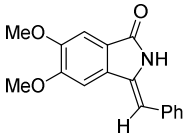
3g (71%)



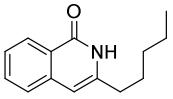
3i (75%)



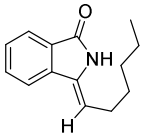
3h (46%)



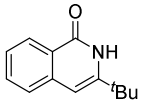
5h (34%)



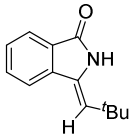
3k (61%)



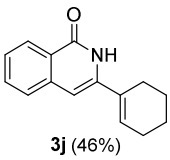
5k (7%)



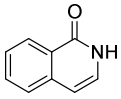
3l (21%)



5l (55%)



3j (46%)

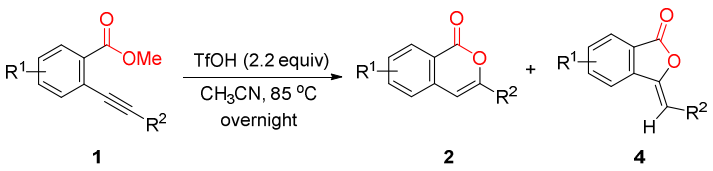


3m (60%)[c]

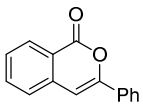
[a] Representative procedure: A 20 mL glass reaction vial was charged with **1** (2.0 mmol, 1.0 equiv), triflic acid (663.1 mg, 4.4 mmol, 2.2 equiv) and acetonitrile (10 mL). The vial was flushed with nitrogen and sealed with a pressure relief cap. The reaction mixture was stirred at 85 °C overnight, until the disappearance of starting material **1** was observed. The reaction mixture was cooled to room temperature and piperidine (340.6 mg, 4.0 mmol, 2.0 equiv) was added, while stirring continued for 30 min. The solvent was evaporated using a rotary evaporator. Ammonium acetate (462.5 mg, 6.0 mmol, 3.0 equiv) and DMAc (5 mL) were then added to the reaction. The resulting reaction mixture was heated at 120 °C overnight, until the disappearance of intermediate **2** was observed. [b] Isolated yields after column chromatography. [c] Product **3m** was prepared from methyl 2-((trimethylsilyl)ethynyl)benzoate (**1m**) in the presence of $NaAuCl_4$ (10 mol%) / $AgSbF_6$ (10 mol%) and 1.1 equiv TfOH. For details, see the experimental section.

Isochromen-1-ones (**2**) were the key intermediate compounds in this one-pot reaction. Their synthesis had also attracted plenty of interest.[24] We, therefore, decided to isolate the isochromen-1-ones (**2**) after the completion of the first step. The isochromen-1-ones (**2**) were obtained in moderate to good yields (Table 4). It is worth noting that the same substituent-induced regioselectivity pattern was also observed in the isochromen-1-one formation. A pair of regioisomers of isochromen-1-ones (**2**) and isobenzofuran-1-ones (**4**) were obtained, when 1) the distal group (R^2) on the alkyne bond was an alkyl (Table 4, **2k**, **4k 2l**, and **4l**); 2) an electron-donating group was present at the *para*-position on the proximal phenyl ring (**2d**, **4d**, **2h**, and **4h**); and 3) an electron-withdrawing group was present at the *para*-position on the distal phenyl ring (**2c** and **4c**). A similar substituent effect was also observed by the Abbiati group.[24b] Cyclization of methyl 2-((trimethylsilyl)ethynyl)benzoate (**1m**) was carried out in the presence of $NaAuCl_4$ (10 mol%) / $AgSbF_6$ (10 mol%) and 1.1 equiv TfOH, and isochromen-1-one (**2m**) was obtained in 69% yield. On the other hand, the cyclization of **1m** failed under the conditions listed in Table 4.

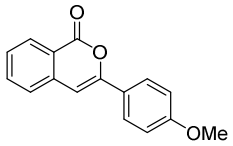
Table 4. Triflic Acid Mediated Intramolecular Cyclization of *ortho*-Alkynylarylesters[a]



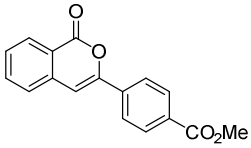
1 2 4



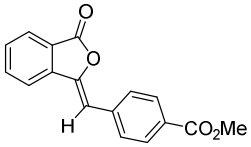
2a (84%)



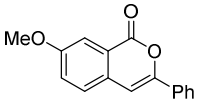
2b (82%)



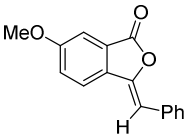
2c (60%)



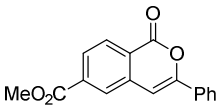
4c (20%)



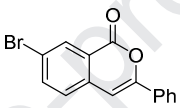
2d (21%)



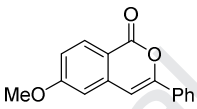
4d (58%)



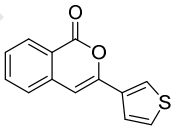
2e (81%)



2f (85%)



2g (88%)



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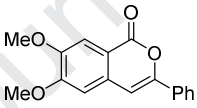
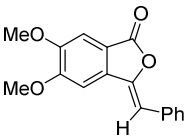
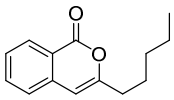


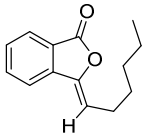
2h (51%)



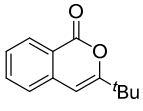
4h (39%)



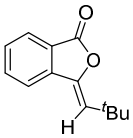
2k (73%)



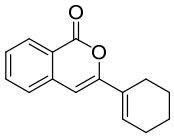
4k (11%)



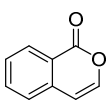
2l (25%)



4l (67%)



2j (51%)

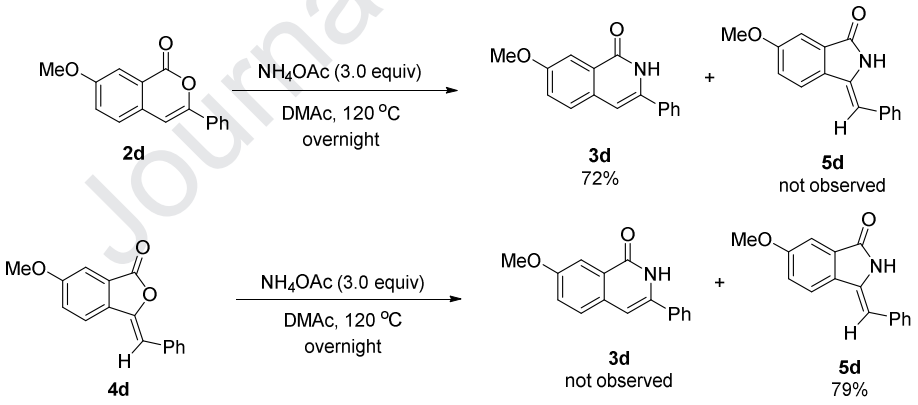


2m (69%)[c]

[a] Representative procedure: A 20 mL glass reaction vial was charged with **1** (2.0 mmol, 1.0 equiv), triflic acid (660.3 mg, 4.4 mmol, 2.2 equiv) and acetonitrile (10 mL). The vial was then flushed with nitrogen and sealed with a pressure relief cap. The reaction mixture was stirred at 85 °C overnight, until the disappearance of starting material **1** was observed. [b] Isolated yields after column chromatography. [c] Product **2m** was prepared from methyl 2-((trimethylsilyl)ethynyl)benzoate (**1m**) in the presence of $NaAuCl_4$ (10 mol%) / $AgSbF_6$ (10 mol%) and 1.1 equiv TfOH. For details, see the experimental section.

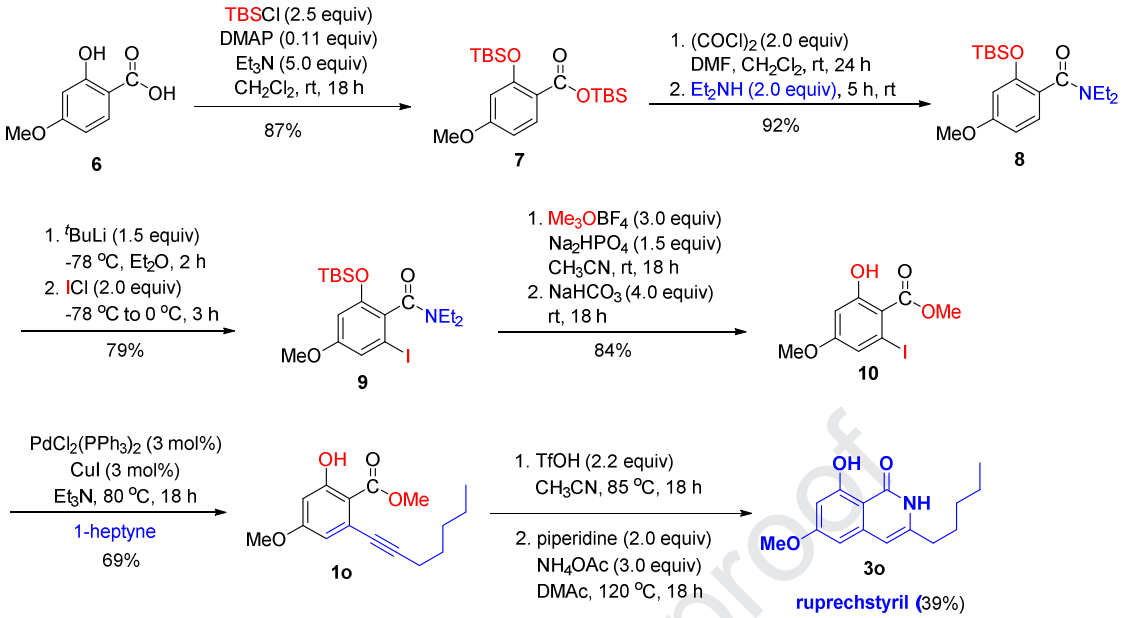
We next examined interconversion reactions of isochromen-1-one (**2d**) and isobenzofuran-1-one (**4d**) in the presence of 3.0 equiv NH_4OAc in DMAc. It turned out that in the NH_4OAc participated substitution reaction isochromen-1-ones (**2d**) solely led to isoquinolin-1-one (**3d**) and isobenzofuran-1-one (**4d**) exclusively led to isoindolin-1-one (**5d**) (Scheme 2). No interconversion between the five-membered and six-membered ring products was observed during the substitution step. These results showed that the regioselectivity observed in the one-pot protocol was determined in the triflic acid mediated *ortho*-alkynylarylester cyclization step.

Scheme 2. Interconversion experiments



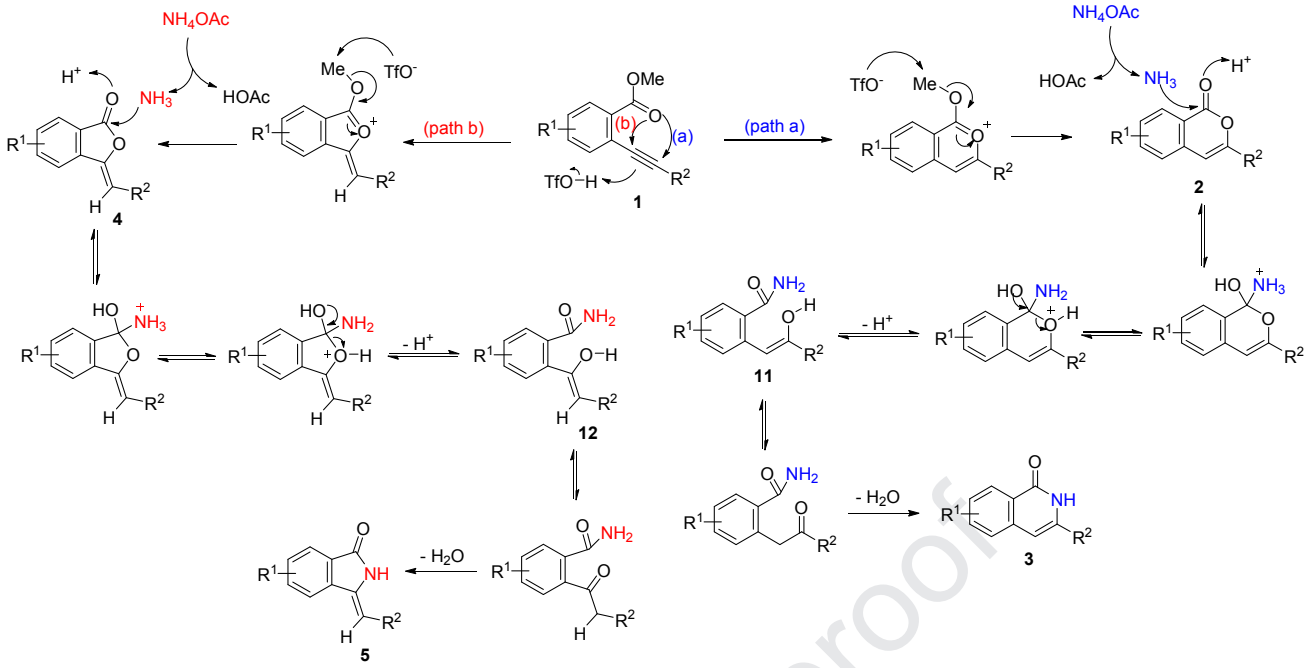
We further applied the one-pot reaction protocol in the synthesis of a natural product – ruprechstyril[25] (**3o**, Scheme 3). We started from commercially available 2-hydroxy-4-methoxybenzoic acid (**6**), and prepared methyl 2-hydroxy-6-iodo-4-methoxybenzoate (**10**) referring a literature procedure.[26] After a Sonogashira coupling, **10** was converted to **1o**. The latter was then subjected to our one-pot cyclization condition, and ruprechstyril (**3o**) was prepared in 39% yield.

Scheme 3. Synthesis of Ruprechstyril



The one-pot reaction presumably starts from a Brønsted acid mediated *6-endo-dig* cyclization of *ortho*-alkynylarylester **1** (Scheme 4, path a), leading to isochromenone **2**. An NH_4OAc participated substitution then takes place, via a ring opening to form intermediate **11**. Subsequent tautomerization, ring closure and dehydration lead to isoquinolinone **3**. On the other hand, when 1) the distal group (R^2) on the alkyne bond is an alkyl; 2) an electron-donating group is present at the *para*-position on the proximal phenyl ring; and 3) an electron-withdrawing group is present at the *para*-position on the distal phenyl ring, the α-carbon (proximal alkyne carbon) bears more positive character (becoming more electrophilic), which leads to a competitive *5-exo-dig* cyclization affording isobenzofuranone **4** (Scheme 4, path b). The latter undergoes an NH_4OAc participated substitution and a subsequent ring opening to form intermediate **12**. After tautomerization, ring closure and dehydration, **12** converts to isoindolinone **5**.

Scheme 4. Proposed Mechanism for the Triflic Acid Mediated One-Pot Reaction



Conclusion

A Brønsted acid mediated one-pot reaction of *ortho*-alkynylarylesters and ammonium acetate is reported. The reaction leads to isoquinolinones in general. With specified substitution pattern on the *ortho*-alkynylarylesters, a pair of regioisomers – isoindolinones and isoquinolinones were both obtained. The intermediate compounds isochromenones and isobezofurans were also isolated in good yields. Interconversion reactions of a sample isochromenone and isobenzofuran showed that the regioselectivity was determined in the step of triflic acid induced cyclization of *ortho*-alkynylarylesters, and the NH_4OAc participated substitution did not result in isomerization between the five-membered and six-membered ring products. The method was employed in the synthesis of a natural product – ruprechstyril, affording a moderate yield. Further application of NH_4OAc in the synthesis of nitrogen-containing heterocycles is underway in our laboratory and will be reported in due course.

Experimental section

General information.

All reactions were carried out in sealed 20 mL glass reaction vials with pressure relief caps, unless otherwise indicated. All commercially available chemicals were used as received without further

purification unless otherwise noted. All ^{1}H and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz respectively, using $CDCl_3$ or DMSO-d_6 as the solvent. The chemical shifts of all ^{1}H and ^{13}C NMR spectra are referenced to the residual signal of $CDCl_3$ (δ 7.26 ppm for the ^{1}H NMR spectra and δ 77.23 ppm for the ^{13}C NMR spectra) or DMSO-d_6 (δ 2.50 ppm for the ^{1}H NMR spectra and δ 39.51 ppm for the ^{13}C NMR spectra). The high-resolution mass analysis was carried out on high resolution mass spectrometers using heated electrospray ionization (HESI) method. Samples were dissolved in methylene chloride and methanol and analyzed via flow injection into the mass spectrometer at a flow rate of 200 µL/min. The mobile phase was 90:10 methanol:water. The melting points are uncorrected.

General procedure for the preparation of 2-alkynylarylesters

A 20 mL glass reaction vial was charged with 2-bromoarylester (2.0 mmol, 1.0 equiv), a terminal alkyne (2.2 mmol, 1.1 equiv), bis(triphenylphosphine)palladium(II) dichloride (28.1 mg, 0.04 mmol, 2 mol%), copper iodide (7.6 mg, 0.04 mmol, 2 mol%), and triethylamine (10 mL). The vial was then flushed with nitrogen and sealed. The reaction mixture was stirred at 80 °C overnight, until the disappearance of the starting material was observed, as monitored by thin layer chromatography. The reaction mixture was diluted with diethyl ether (40 mL), washed with brine (40 mL), and the aqueous phase was extracted with diethyl ether (2 × 20 mL). The combined organic layers were dried over anhydrous magnesium sulfate, concentrated using a rotary evaporator under reduced pressure (20 mmHg); the resulting residue was purified by flash column chromatography on silica gel (eluent: hexane/ethyl acetate).

Methyl 2-(phenylethynyl)benzoate (1a)

This product was obtained as an orange oil (458.4 mg, 97% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.61 (dd, *J* = 7.7, 0.8 Hz, 1H), 7.57–7.60 (m, 2H), 7.50 (td, *J* = 7.7, 1.3 Hz, 1H), 7.41–7.35 (m, 4H), 3.97 (s, 3H). The ^{1}H NMR spectral data are in good agreement with the literature data.[27]

Methyl 2-((4-methoxyphenyl)ethynyl)benzoate (1b)

This product was obtained as a light yellow solid (447.4 mg, 84% yield); mp = 75–76 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (dd, *J* = 7.9, 0.8 Hz, 1H), 7.60 (dd, *J* = 7.7, 0.6 Hz, 1H), 7.52 (d, *J* = 8.8 Hz, 2H), 7.43 (td, *J* = 7.7, 1.2 Hz, 1H), 7.31 (td, *J* = 7.8, 1.2 Hz, 1H), 6.86 (d, *J* = 8.8 Hz, 2H), 3.93 (s, 3H), 3.77 (s, 3H). The ^{1}H NMR spectral data are in good agreement with the literature data.[28]

Methyl 2-((4-(methoxycarbonyl)phenyl)ethynyl)benzoate (1c)

This product was obtained as a yellow solid (559.2 mg, 95% yield); mp = 77–78 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (dm, *J* = 8.4 Hz, 2H), 7.91 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.56–7.58 (m, 3H), 7.41 (td, *J* = 7.6, 1.3 Hz, 1H), 7.31 (td, *J* = 7.7, 1.2 Hz, 1H), 3.88 (s, 3H), 3.83 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.4, 166.2, 134.1, 131.81, 131.76, 131.6, 130.5, 129.6, 129.5, 128.4, 128.0, 123.1, 93.4, 91.2, 52.2, 52.1; HRMS (HESI-ORBITRAP) *m/z* $[M + Na]^+$ calcd for $(C_{18}H_{14}O_4Na)^+$ 317.0784, found 317.0780; IR (neat) ν_{max} 1719, 1707, 1603, 1565, 1479, 1433, 1405, 1289, 1272, 1249, 1169, 1193, 1127, 1104, 1076, 1016, 962, 853, 767, 753, 692 cm^{-1}.

Methyl 5-methoxy-2-(phenylethynyl)benzoate (1d)

This product was obtained as an orange oil (314.2 mg, 59% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58–7.53 (m, 3H), 7.49 (d, *J* = 2.8 Hz, 1H), 7.32–7.37 (m, 3H), 7.04 (dd, *J* = 8.6, 2.8 Hz, 1H), 3.97 (s, 3H), 3.87 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.8, 159.3, 135.6, 133.4, 131.8, 128.5, 128.4, 123.8, 118.6, 116.1, 115.2, 92.8, 88.4, 55.8, 52.5; HRMS (HESI-ORBITRAP) *m/z* $[M + H]^+$ calcd for $(C_{17}H_{15}O_3)^+$ 267.1016, found 267.1009; IR (neat) ν_{max} 2948, 2837, 1729, 1713, 1594, 1557, 1499, 1434, 1326, 1287, 1245, 1216, 1182, 1070, 1032, 979, 894, 824, 780, 754, 689 cm^{-1}.

Dimethyl 2-(phenylethynyl)terephthalate (1e)

This product was obtained as a white solid (547.4 mg, 93% yield); mp = 93–94 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (dd, *J* = 1.3, 0.8 Hz, 1H), 8.01–8.02 (m, 2H), 7.58–7.60 (m, 2H), 7.36–7.39 (m, 3H), 3.99 (s, 3H), 3.96 (s, 3H). The ^{1}H NMR spectral data are in good agreement with the literature data.[29]

Methyl 5-bromo-2-(phenylethynyl)benzoate (1f)

This product was obtained as a white solid (479.1 mg, 76% yield); mp = 70–71 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 2.0 Hz, 1H), 7.53–7.57 (m, 3H), 7.50 (d, *J* = 8.3 Hz, 1H), 7.31–7.34 (m, 3H), 3.93 (s, 3H). The ^{1}H NMR spectral data are in good agreement with the literature data.[30]

Methyl 4-methoxy-2-(phenylethynyl)benzoate (1g)

This product was obtained as an orange oil (527.3 mg, 99% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 1.8 Hz, 1H), 7.58–7.61 (m, 2H), 7.35–7.37 (m, 3H), 7.13 (d, *J* = 2.7 Hz, 1H), 6.89 (dd, *J* = 8.8, 2.7 Hz, 1H), 3.93 (s, 3H), 3.87 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.4, 162.2, 132.9, 132.0, 128.8, 128.6, 125.9, 124.2, 123.5, 118.6, 114.6, 94.4, 88.6, 55.8, 52.1; HRMS (HESI-ORBITRAP) *m/z* $[M + H]^+$ calcd for $(C_{17}H_{15}O_3)^+$ 267.1016, found 267.1011; IR (neat) ν_{max} 2948, 2838, 2212, 1725, 1597, 1564, 1500, 1434, 1337, 1290, 1257, 1234, 1185, 1124, 1084, 1032, 777, 756, 691 cm^{-1}.

Methyl 4,5-dimethoxy-2-(phenylethynyl)benzoate (1h)

This product was obtained as an orange solid (586.7 mg, 99% yield); mp = 114–116 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54–7.57 (m, 2H), 7.47 (s, 1H), 7.29–7.34 (m, 3H), 7.04 (s, 1H), 3.91 (s, 3H), 3.90 (s, 6H). The ^{1}H NMR spectral data are in good agreement with the literature data.[29]

Methyl 2-(thiophen-3-ylethynyl)benzoate (1i)

This product was obtained as an orange oil (460.4 mg, 95% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.63 (dd, *J* = 7.8, 0.9 Hz, 1H), 7.57 (dd, *J* = 3.0, 1.2 Hz, 1H), 7.48 (td, *J* = 7.7, 1.4 Hz, 1H), 7.37 (td, *J* = 7.6, 1.3 Hz, 1H), 7.31 (dd, *J* = 5.0, 3.0 Hz, 1H), 7.24 (dd, *J* = 5.0, 1.2 Hz, 1H), 3.97 (s, 3H). The ^{1}H NMR spectral data are in good agreement with the literature data. [31]

Methyl 2-(cyclohex-1-en-1-ylethynyl)benzoate (1j)

This product was obtained as an orange oil (259.5 mg, 54% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.52 (dd, *J* = 7.8, 1.0 Hz, 1H), 7.43 (td, *J* = 7.7, 1.4 Hz, 1H), 7.31 (td, *J* = 7.7, 1.3 Hz, 1H), 6.26–6.29 (m, 1H), 3.92 (s, 3H), 2.24–2.28 (m, 2H), 2.13–2.18 (m, 2H), 1.66–1.72 (m, 2H), 1.59–1.65 (m, 2H). The ^{1}H NMR spectral data are in good agreement with the literature data.[32]

Methyl 2-(hept-1-yn-1-yl)benzoate (1k)

This product was obtained as a yellow oil (382.3 mg, 83% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (dd, *J* = 7.9, 0.8 Hz, 1H), 7.50 (d, *J* = 7.8 Hz, 1H), 7.41 (td, *J* = 7.7, 1.3 Hz, 1H), 7.30 (td, *J* = 7.8, 1.1 Hz, 1H), 3.91 (s, 3H), 2.47 (t, *J* = 7.1 Hz, 2H), 1.64 (m, *J* = 7.6 Hz, 2H), 1.42–1.49 (m, 2H), 1.32–1.40 (m, 2H), 0.92 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 167.2, 134.4, 132.1, 131.6, 130.3, 127.3, 124.7, 96.2, 79.4, 52.3, 31.3, 28.6, 22.5, 20.0, 14.2; HRMS (HESI-ORBITRAP) *m/z* $[M + H]^+$ calcd for $(C_{15}H_{19}O_2)^+$ 231.1380, found 231.1378; IR (neat) ν_{max} 2932, 2860, 2235, 1734, 1596, 1566, 1484, 1447, 1432, 1329, 1293, 1250, 1190, 1162, 1129, 1083, 1043, 963, 757, 702 cm^{-1}.

Methyl 2-(3,3-dimethylbut-1-yn-1-yl)benzoate (1l)

This product was obtained as an orange oil (410.9 mg, 95% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.48 (dd, *J* = 7.7, 0.9 Hz, 1H), 7.40 (td, *J* = 7.7, 1.4 Hz, 1H), 7.30 (td, *J* = 7.7, 1.3 Hz, 1H), 3.92 (s, 3H), 1.34 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 167.5, 134.1, 132.4, 131.6, 130.4, 127.3, 124.4, 103.8, 78.0, 52.1, 31.1, 28.4; HRMS (HESI-ORBITRAP) *m/z* $[M + H]^+$ calcd for $(C_{14}H_{17}O_2)^+$ 217.1223, found: 217.1218; IR (neat) ν_{max} 3066, 2969, 2982, 2902, 2867, 2239, 1732, 1596, 1567, 1484, 1475, 1447, 1432, 1362, 1290, 1249, 1201, 1128, 1081, 1041, 966, 824, 785, 757, 702 cm^{-1}.

Methyl 2-((trimethylsilyl)ethynyl)benzoate (1m)

This product was obtained as an orange oil (446.1 mg, 96% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (dd, *J* = 7.8, 1.0 Hz, 1H), 7.58 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.44 (td, *J* = 7.6, 1.5 Hz, 1H), 7.36 (td, *J* = 7.6, 1.4 Hz, 1H), 3.92 (s, 3H), 0.27 (s, 9H). The ^{1}H NMR spectral data are in good agreement with the literature data.[31]

Methyl 2-(hept-1-yn-1-yl)-6-hydroxy-4-methoxybenzoate (1o)

This product was obtained as a yellow wax (381.3 mg, 69% yield); mp = 41–42 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.65 (s, 1H), 6.60 (d, *J* = 2.6 Hz, 1H), 6.41 (d, *J* = 2.6 Hz, 1H), 3.93 (s, 3H), 3.80 (s, 3H), 2.45 (t, *J* = 7.1 Hz, 2H), 1.60–1.66 (m, 2H), 1.41–1.49 (m, 2H), 1.34–1.39 (m,

2H), 0.93 (t, *J* = 7.2 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 171.2, 164.7, 163.9, 126.8, 114.2, 106.4, 101.4, 95.9, 80.2, 55.7, 52.1, 31.4, 28.6, 22.5, 20.0, 14.2; HRMS (HESI-ORBITRAP) *m/z* $[M + H]^+$ calcd for $(C_{16}H_{21}O_4)^+$ 277.1434, found 277.1431; IR (neat) ν_{max} 2949, 1935, 2866, 1650, 1601, 1568, 1432. 1330, 1309, 1253, 1162, 1040, 982, 871, 730 cm^{-1}.

General procedure for the TfOH mediated intramolecular cyclization of 2-alkynylarylesters

A 20 mL glass reaction vial was charged with 2-alkynylarylester (**1**, 2.0 mmol, 1.0 equiv), triflic acid (660.4 mg, 4.4 mmol, 2.2 equiv), and acetonitrile (10 mL). The vial was then flushed with nitrogen and sealed. The reaction mixture was stirred at 85 °C overnight, until the disappearance of the starting material (**1**) was observed, as monitored by thin layer chromatography. The reaction mixture was diluted with ethyl acetate (40 mL) and washed with brine (40 mL). The aqueous phase was then extracted with ethyl acetate (2 × 20 mL). The combined organic layers were dried over anhydrous magnesium sulfate, concentrated using a rotary evaporator under reduced pressure (20 mmHg). The resulting residue was purified by flash column chromatography on silica gel (eluent: hexane/ethyl acetate or dichloromethane/hexane).

3-Phenyl-1*H*-isochromen-1-one (2a)

This product was obtained as a beige solid (373.4 mg, 84% yield); mp = 83–84 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, *J* = 8.2 Hz, 1H), 7.79 (dd, *J* = 7.9, 1.6 Hz, 2H), 7.63 (td, *J* = 7.8, 1.2 Hz, 1H), 7.36–7.42 (m, 5H), 6.85 (s, 1H). The ^{1}H NMR spectral data are in good agreement with the literature data.[33]

3-(4-Methoxyphenyl)-1*H*-isochromen-1-one (2b)

This product was obtained as a white solid (413.8 mg, 82% yield); mp = 122–123 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.13 Hz, 1H), 7.71 (dm, *J* = 8.9 Hz, 2H), 7.60 (td, *J* = 7.6, 1.2 Hz, 1H), 7.35–7.38 (m, 2H), 6.87 (dm, *J* = 8.9 Hz, 2H), 6.71 (s, 1H), 3.77 (s, 3H). The ^{1}H NMR spectral data are in good agreement with the literature data.[33]

Methyl 4-(1-oxo-1*H*-isochromen-3-yl)benzoate (2c)

This product was obtained as a white solid (336.3 mg, 60% yield); mp = 194–195 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 8.1 Hz, 1H), 8.07 (dm, *J* = 8.6 Hz, 2H), 7.89 (dm, *J* = 8.6 Hz, 2H), 7.71 (td, *J* = 7.8, 1.2 Hz, 1H), 7.48–7.51 (m, 2H), 7.01 (s, 1H), 3.92 (s, 3H). The ^{1}H NMR spectral data are in good agreement with the literature data.[20a]

Methyl (*Z*)-4-((3-oxoisobenzofuran-1(3*H*)-ylidene)methyl)benzoate (4c)

This product was obtained as a white solid (112.1 mg, 20% yield); mp = 183–184 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (dm, *J* = 8.4 Hz, 2H), 7.92 (d, *J* = 7.7 Hz, 1H), 7.86 (dm, *J* = 8.4 Hz, 2H), 7.71–7.78 (m, 2H), 7.56 (td, *J* = 7.4, 1.0 Hz, 1H), 6.40 (s, 1H), 3.91 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.8, 146.3, 140.4, 137.7, 134.9, 130.5, 130.1, 130.0, 129.5, 125.9, 123.7, 120.3, 105.9, 52.4 (fewer ^{13}C signals were observed due to signal overlapping); HRMS (HESI-ORBITRAP) *m/z* $[M + H]^+$ calcd for $(C_{17}H_{13}O_4)^+$ 281.0808, found 281.0804; IR (neat) ν_{max} 1797, 1719, 1606, 1472, 1430, 1281, 1184, 1108, 1078, 971, 866, 766, 695 cm^{-1}.

7-Methoxy-3-phenyl-1*H*-isochromen-1-one (2d)

This product was obtained as a beige solid (105.9 mg, 21% yield); mp = 164–165 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (dd, *J* = 7.0, 1.6 Hz, 2H), 7.72 (d, *J* = 2.7 Hz, 1H), 7.40–7.47 (m, 4H), 7.31 (dd, *J* = 8.6, 2.7 Hz, 1H), 6.93 (s, 1H), 3.92 (s, 3H). The ^{1}H NMR spectral data are in good agreement with the literature data. [34]

(*Z*)-3-Benzylidene-6-methoxyisobenzofuran-1(3*H*)-one (4d)

This product was obtained as a beige solid (292.6 mg, 58% yield); mp = 134–135 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (dd, *J* = 7.4, 1.2 Hz, 2H); 7.60 (d, *J* = 8.5 HZ, 1H), 7.35 (t, *J* = 7.6 Hz, 2H), 7.26–7.27 (m, 1H), 7.23–7.24 (m, 1H), 7.21–7.22 (m, 1H), 6.23 (s, 1H), 3.84 (s, 3H). The 1H NMR spectral data are in good agreement with the literature data.[35]

Methyl 1-oxo-3-phenyl-1*H*-isochromene-6-carboxylate (2e)

This product was obtained as a yellow solid (454.1 mg, 81% yield); mp = 202–203 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, *J* = 8.3 Hz, 1H), 8.18 (d, *J* = 1.2 Hz, 1H), 8.09 (dd, *J* = 8.2, 1.5 Hz, 1H), 7.87–

7.89 (m, 2H), 7.46–7.48 (m, 3H), 7.00 (s, 1H), 3.99 (s, 3H). The ^{1}H NMR spectral data are in good agreement with the literature data.[36]

7-Bromo-3-phenyl-1*H*-isochromen-1-one (2f)

This product was obtained as a white solid (511.9 mg, 85% yield); mp = 187–189 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, *J* = 2.0 Hz, 1H), 7.84–7.87 (m, 2H), 7.80 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.45–7.46 (m, 3H), 7.37 (d, *J* = 8.4 Hz, 1H), 6.91 (s, 1H). The ^{1}H NMR spectral data are in good agreement with the literature data.[24c]

6-Methoxy-3-phenyl-1*H*-isochromen-1-one (2g)

This product was obtained as a white solid (444.0 mg, 88% yield); mp = 140–141 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.8 Hz, 1H), 7.82–7.84 (m, 2H), 7.39–7.45 (m, 3H), 6.98 (dd, *J* = 8.8, 2.3 Hz, 1H), 6.82–6.83 (m, 2H), 3.88 (s, 3H). The ^{1}H NMR spectral data are in good agreement with the literature data.[37]

6,7-Dimethoxy-3-phenyl-1*H*-isochromen-1-one (2h)

This product was obtained as an orange solid (287.9 mg, 51% yield); mp = 163–164 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82–7.84 (m, 2H), 7.64 (s, 1H), 7.39–7.45 (m, 3H), 6.87 (s, 1H), 6.85 (s, 1H), 4.00 (s, 3H), 3.97 (s, 3H). The ^{1}H NMR spectral data are in good agreement with the literature data.[33]

(*Z*)-3-Benzylidene-5,6-dimethoxyisobenzofuran-1(3*H*)-one (4h)

This product was obtained as a white solid (220.2 mg, 39% yield); mp = 198–199 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81–7.83 (m, 2H), 7.38–7.42 (m, 2H), 7.27–7.32 (m, 2H), 7.12 (s, 1H), 6.28 (s, 1H), 4.05 (s, 3H), 3.96 (s, 3H). The 1H NMR spectral data are in good agreement with the literature data.[35]

3-(Thiophen-3-yl)-1*H*-isochromen-1-one (2i)

This product was obtained as a white solid (369.8 mg, 81% yield); mp = 113–114 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 7.9 Hz, 1H), 7.74 (dd, *J* = 2.8, 1.2 Hz, 1H), 7.58 (td, *J* = 7.6, 1.0 Hz, 1H),

7.28–7.37 (m, 4H), 6.64 (s, 1H). The ^{1}H NMR spectral data are in good agreement with the literature data.[38]

3-(Cyclohex-1-en-1-yl)-1*H*-isochromen-1-one (2j)

This product was obtained as a yellow solid (230.8 mg, 51% yield); mp = 81–82 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 7.9 Hz, 1H), 7.60 (td, *J* = 7.8, 1.2 Hz, 1H), 7.33–7.39 (m, 2H), 6.75–6.78 (m, 1H), 6.30 (s, 1H), 2.21–2.24 (m, 4H), 1.70–1.76 (m, 2H), 1.59–1.64 (m, 2H). The ^{1}H NMR spectral data are in good agreement with the literature data.[24a]

3-Pentyl-1*H*-isochromen-1-one (2k)

This product was obtained as a yellow oil (315.8 mg, 73% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, *J* = 8.0 Hz, 1H), 7.66 (td, *J* = 7.9, 1.2 Hz, 1H), 7.44 (td, *J* = 7.6, 0.9 Hz, 1H), 7.34 (d, *J* = 7.9 Hz, 1H), 6.25 (s, 1H), 2.51 (t, *J* = 7.6 Hz, 2H), 1.67–1.72 (m, 2H), 1.32–1.37 (m, 4H), 0.90 (t, *J* = 7.0 Hz, 3H). The ^{1}H NMR spectral data are in good agreement with the literature data.[39]

(*Z*)-3-Hexylideneisobenzofuran-1(3*H*)-one (4k)

This product was obtained as a yellow oil (47.6 mg, 11% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 7.7 Hz, 1H), 7.62–7.68 (m, 2H), 7.49 (t, *J* = 7.2 Hz, 1H), 5.63 (t, *J* = 7.8 Hz, 1H), 2.46 (q, *J* = 7.6 Hz, 2H), 1.52 (p, *J* = 7.2 Hz, 2H), 1.33–1.35 (m, 4H), 0.89 (t, *J* = 6.7 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 167.4, 145.8, 139.8, 134.4, 129.5, 125.4, 124.6, 119.8, 110.0, 31.7, 29.1, 26.0, 22.7, 14.2; HRMS (HESI-ORBITRAP) *m/z* $[M + H]^+$ calcd for $(C_{14}H_{17}O_2)^+$ 217.1223, found 217.1220; IR (neat) ν_{max} 2956, 2929, 2870, 1773, 1697, 1584, 1402, 1258, 1069, 910, 795, 767, 735, 695, 673 cm^{-1}.

3-(*tert*-Butyl)-1*H*-isochromen-1-one (2l)

This product was obtained as a yellow oil (101.1 mg, 25% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (dm, *J* = 8.0 Hz, 1H), 7.67 (td, *J* = 7.8, 1.3 Hz, 1H), 7.49 (td, *J* = 7.6, 1.3 Hz, 1H), 7.38 (d, *J* = 7.9 Hz, 1H), 6.30 (s, 1H), 1.32 (s, 9H). The ^{1}H NMR spectral data are in good agreement with the literature data.[24a]

(*Z*)-3-(2,2-Dimethylpropylidene)isobenzofuran-1(3*H*)-one (4l)

This product was obtained as a beige solid (271.0 mg, 67% yield); mp = 86–87 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (dm, *J* = 7.7 Hz, 1H), 7.59–7.67 (m, 2H), 7.48 (td, *J* = 7.4, 1.2 Hz, 1H), 5.59 (s, 1H), 1.31 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 167.4, 143.8, 140.9, 134.3, 129.5, 125.3, 123.7, 119.7, 118.9, 32.8, 30.7; HRMS (HESI-ORBITRAP) *m/z* $[M + H]^+$ calcd for $(C_{13}H_{15}O_2)^+$ 203.1067, found 203.1061; IR (neat) ν_{max} 2955, 2866, 1768, 1722, 1676, 1647, 1469, 1344, 1299, 1266, 1197, 1083, 986, 830, 763, 689 cm^{-1}.

1*H*-Isochromen-1-one (2m)

A 20 mL glass reaction vial was charged with **1m** (532.0 mg, 2.289 mmol, 1.0 equiv), sodium tetrachloroaurate dihydrate (91.0 mg, 0.229 mmol, 0.1 equiv), silver hexafluoroantimonate (79.0 mg, 0.229 mmol, 0.1 equiv), anhydrous acetonitrile (10 mL) and triflic acid (377.0 mg; 2.515 mmol; 1.1 equiv). The vial was purged with argon and sealed. The reaction mixture was stirred at 85 °C for 6 h. After cooling to room temperature, the resulting mixture was diluted with ethyl acetate (15 mL) and washed with brine (15 mL). The aqueous phase was extracted with ethyl acetate (2 × 10 mL). The combined organic layers were dried over anhydrous magnesium sulfate, and concentrated using a rotary evaporator, under reduced pressure (20 mmHg). The residue was purified by flash column chromatography on silica gel (eluent: hexanes/ethyl acetate). This product was obtained as a yellow solid (230.8 mg, 69% yield); mp = 47-49 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 (dt, *J* = 7.9, 0.6 Hz, 1H), 7.73 (dt, *J* = 7.6, 1.3 Hz, 1H), 7.53 (dt, *J* = 8.2, 1.1 Hz, 1H), 7.44 (d, *J* = 7.9 Hz, 1H), 7.28 (d, *J* = 5.6 Hz, 1H), 6.51 (d, *J* = 5.6 Hz, 1H). The ^{1}H NMR spectral data are in good agreement with the literature data.[16b]

General procedure for the TfOH mediated one-pot reaction of 2-alkynylarylesters and ammonium acetate

A 20 mL glass reaction vial was charged with 2-alkynylarylester (**1**, 2.0 mmol, 1.0 equiv), triflic acid (660.4 mg, 4.4 mmol, 2.2 equiv) and acetonitrile (10 mL). The vial was then flushed with nitrogen and sealed. The reaction mixture was stirred at 85 °C overnight, until the disappearance of the starting material (**1**) was observed, as monitored by thin layer chromatography.

After completion, the reaction mixture was cooled down to room temperature and piperidine (340.8 mg, 4.0 mmol, 2.0 equiv) was added while stirring continued for 30 min. The solvent was removed using a rotary evaporator under reduced pressure (20 mmHg). Ammonium acetate (462.0 mg, 6.0 mmol, 3.0 equiv) and *N*,*N*-dimethylacetamide (5 mL) were then added to the reaction vial. The resulting reaction mixture was heated at 120 °C overnight, until the disappearance of the intermediate (**2**) was observed, as monitored by thin layer chromatography. The reaction mixture was diluted with ethyl acetate (40 mL) and washed with brine (40 mL), and the aqueous phase was extracted with ethyl acetate (2 × 20 mL). The combined organic layers were dried over anhydrous magnesium sulfate, concentrated using a rotary evaporator under reduced pressure (20 mmHg). The resulting residue was purified by flash column chromatography on silica gel (eluent: hexane/ethyl acetate).

3-Phenylisoquinolin-1(2*H*)-one (3a)

This product was obtained as a white solid (331.9 mg, 75% yield); mp = 198–199 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.71 (s, 1H), 8.41 (d, *J* = 8.0 Hz, 1H), 7.78–7.80 (m, 2H), 7.68 (td, *J* = 7.2, 1.4 Hz, 1H), 7.60 (d, *J* = 7.7 Hz, 1H), 7.45–7.55 (m, 4H), 6.80 (s, 1H). The ^{1}H NMR spectral data are in good agreement with the literature data.[16e]

3-(4-Methoxyphenyl)isoquinolin-1(2*H*)-one (3b)

This product was obtained as a white solid (341.5 mg, 68%) yield; mp = 238–239 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.45 (s, 1H), 8.18 (d, *J* = 7.8 Hz, 1H), 7.75 (d, *J* = 8.8 Hz, 2H), 7.68–7.69 (m, 2H), 7.45 (ddd, *J* = 8.2, 5.9, 2.4 Hz, 1H), 7.04 (d, *J* = 8.8 Hz, 2H), 6.84 (s, 1H), 3.82 (s, 3H). The ^{1}H NMR spectral data are in good agreement with the literature data.[16e]

Methyl 4-(1-oxo-1,2-dihydroisoquinolin-3-yl)benzoate (3c)

This product was obtained as a white solid (284.8 mg, 51% yield); mp = 270–271 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.65 (s, 1H), 8.22 (d, *J* = 7.8 Hz, 1H), 8.05 (d, *J* = 8.5 Hz, 2H), 7.95 (d, *J* = 8.6 Hz, 2H), 7.75 (dd, *J* = 4.7, 1.0 Hz, 2H), 7.53 (ddd, *J* = 8.2, 4.8, 3.5 Hz, 1H), 7.06 (s, 1H), 3.89 (s, 3H). The ^{1}H NMR spectral data are in good agreement with the literature data.[20a]

Methyl (*Z*)-4-((3-oxoisoindolin-1-ylidene)methyl)benzoate (5c)

This product was obtained as an orange solid (83.8 mg, 15% yield); mp = 163–164 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.88 (s, 1H), 8.09 (d, *J* = 7.8 Hz, 1H), 7.96 (d, *J* = 8.4 Hz, 2H), 7.71–7.79 (m, 4H), 7.59 (t, *J* = 7.4 Hz, 1H), 6.84 (s, 1H), 3.87 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 169.2, 166.0, 139.5, 138.6, 134.5, 132.5, 129.7, 129.5, 129.2, 128.3, 127.6, 122.8, 120.7, 104.5, 52.1; HRMS (HESI-ORBITRAP) *m/z* [M + H]$^{+}$ calcd for $(C_{17}H_{14}NO_3)^{+}$ 280.0968, found 280.0962; IR (neat) ν_{max} 3205, 2918, 1706, 1685, 1648, 1603, 1441, 1429, 1307, 1272, 1223, 1139, 1113, 1052, 1014, 969, 865, 764, 727, 698, 663 cm^{-1}.

7-Methoxy-3-phenylisoquinolin-1(2*H*)-one (3d)

This product was obtained as a white solid (75.4 mg, 15% yield); mp = 235–236 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.52 (s, 1H), 7.77 (dd, *J* = 7.1, 1.3 Hz, 2H), 7.68 (d, *J* = 8.7 Hz, 1H), 7.63 (d, *J* = 2.6 Hz, 1H), 7.41–7.50 (m, 3H), 7.35 (dd, *J* = 8.7, 2.8 Hz, 1H), 6.92 (s, 1H), 3.88 (s, 3H). The ^{1}H NMR spectral data are in good agreement with the literature data.[40]

(*Z*)-3-Benzylidene-6-methoxyisoindolin-1-one (5d)

This product was obtained as a yellow solid (231.2 mg, 46% yield); mp = 210–211 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.64 (s, 1H), 7.95 (d, *J* = 8.2 Hz, 1H), 7.60 (d, *J* = 7.7 Hz, 2H), 7.39 (t, *J* = 7.2 Hz, 2H), 7.24–7.27 (m, 3H), 6.62 (s, 1H), 3.87 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 168.9, 160.5, 134.9, 132.3, 131.4, 129.9, 128.9, 128.7, 126.9, 121.8, 120.2, 105.6, 104.7, 55.7; HRMS (HESI-ORBITRAP) *m/z* [M + H]$^{+}$ calcd for $(C_{16}H_{14}NO_2)^{+}$ 252.1019, found 252.1013; IR (neat) ν_{max} 1704, 1694, 1648, 1491, 1453, 1403, 1327, 1290, 1243, 1107, 1051, 1020, 908, 877, 825, 785, 750, 723, 689, 634 cm^{-1}.

Methyl 1-oxo-3-phenyl-1,2-dihydroisoquinoline-6-carboxylate (3e)

This product was obtained as a white solid (368.6 mg, 66% yield); mp = 257–258 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.75 (s, 1H), 8.35 (d, *J* = 0.9 Hz, 1H), 8.31 (d, *J* = 8.3 Hz, 1H), 7.96 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.80 (dd, *J* = 7.9, 1.3 Hz, 2H), 7.48–7.54 (m, 3H), 7.10 (s, 1H), 3.92 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 165.8, 162.3, 141.1, 137.9, 133.6, 133.0, 129.5, 128.8, 128.3,

127.6, 127.4, 126.8, 125.8, 103.3, 52.6; HRMS (HESI-ORBITRAP) *m/z* $[M + H]^+$ calcd for $(C_{17}H_{14}NO_3)^+$ 280.0968, found 280.0968; IR (neat) ν_{max} 1722, 1648, 1432, 1246, 1173, 1032 cm^{-1}.

7-Bromo-3-phenylisoquinolin-1(2*H*)-one (3f)

This product was obtained as a yellow solid (432.2 mg, 72% yield); mp = 297–298 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 11.74 (s, 1H), 8.28 (s, 1H), 7.88 (d, *J* = 8.4 Hz, 1H), 7.79 (d, *J* = 6.8 Hz, 2H), 7.70 (d, *J* = 8.5 Hz, 1H), 7.49–7.51 (m, 3H), 6.96 (s, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 161.7, 140.8, 136.9, 135.5, 133.6, 129.5, 129.2, 128.84, 128.81, 126.8, 126.3, 119.1, 102.8; HRMS (HESI-ORBITRAP) *m/z* $[M + H]^+$ calcd for $(C_{15}H_{11}BrNO)^+$ 300.0019, found 300.0013; IR (neat) ν_{max} 1656, 1465, 1285, 1152, 958, 904, 861, 842, 803, 761, 692 cm^{-1}.

6-Methoxy-3-phenylisoquinolin-1(2*H*)-one (3g)

This product was obtained as a white solid (356.8 mg, 71% yield); mp = 245–246 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 11.37 (s, 1H), 8.11 (d, *J* = 8.8 Hz, 1H), 7.77 (dm, *J* = 8.1 Hz, 2H), 7.45–7.52 (m, 3H), 7.18 (d, *J* = 2.3 Hz, 1H), 7.06 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.84 (s, 1H), 3.88 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 162.5, 162.4, 140.6, 140.1, 133.9, 129.3, 128.8, 128.7, 126.6, 118.7, 115.8, 107.6, 103.1, 55.5; HRMS (HESI-ORBITRAP) *m/z* $[M + H]^+$ calcd for $(C_{16}H_{14}NO_2)^+$ 252.1019, found 252.1014; IR (neat) ν_{max} 2972, 1629, 1605, 1505, 1489, 1459, 1373, 1281, 1244, 1195, 1170, 1153, 1102, 1024, 896, 850, 831, 763, 691, 680 cm^{-1}.

6,7-Dimethoxy-3-phenylisoquinolin-1(2*H*)-one (3h)

This product was obtained as a colorless solid (258.8 mg, 46% yield); mp = 231–232 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 11.38 (s, 1H), 7.76 (dd, *J* = 8.4, 1.5 Hz, 2H), 7.58 (s, 1H), 7.41–7.50 (m, 3H), 7.22 (s, 1H), 6.85 (s, 1H), 3.90 (s, 3H), 3.88 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 162.1, 153.3, 148.7, 138.3, 134.1, 133.3, 128.9, 128.8, 126.4, 118.6, 107.2, 106.6, 102.9, 55.7, 55.5; HRMS (HESI-ORBITRAP) *m/z* $[M + H]^+$ calcd for $(C_{17}H_{16}NO_3)^+$ 282.1125, found 282.1125; IR (neat) ν_{max} 2962, 1631, 1610, 1504, 1463, 1260, 1232, 1172, 1100, 997, 870, 764, 692 cm^{-1}.

(*Z*)-3-Benzylidene-5,6-dimethoxyisoindolin-1-one (5h)

This product was obtained as a white solid (191.3 mg, 34% yield); mp = 194–195 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.39 (s, 1H), 7.63 (s, 1H), 7.60 (d, *J* = 7.5 Hz, 2H), 7.39 (t, *J* = 7.7 Hz, 2H), 7.25 (t, *J* = 7.4 Hz, 1H), 7.20 (s, 1H), 6.69 (s, 1H), 3.93 (s, 3H), 3.86 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 169.3, 153.0, 150.5, 135.0, 132.8, 132.8, 128.8, 128.7, 126.9, 120.8, 104.8, 104.2, 102.9, 56.1, 55.8; HRMS (HESI-ORBITRAP) *m/z* [M + H]$^{+}$ calcd for $(C_{17}H_{16}NO_3)^{+}$ 282.1125, found 282.1119; IR (neat) ν_{max} 2944, 1690, 1499, 1357, 1304, 1211, 1161, 1049, 854, 782, 691 cm^{-1}.

3-(Thiophen-3-yl)isoquinolin-1(2*H*)-one (3i)

This product was obtained as a white solid (340.9 mg, 75% yield); mp = 257–258 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.44 (s, 1H), 8.27 (t, *J* = 2.1 Hz, 1H), 8.18 (d, *J* = 8.0 Hz, 1H), 7.66 – 7.77 (m, 4H), 7.46 (ddd, *J* = 8.1, 6.8, 1.5 Hz, 1H), 7.06 (s, 1H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 162.6, 138.0, 135.2, 135.1, 132.7, 127.4, 126.7, 126.5, 126.2, 125.9, 124.8, 123.3, 102.3; HRMS (HESI-ORBITRAP) *m/z* [M + H]$^{+}$ calcd for $(C_{13}H_{10}NOS)^{+}$ 228.0478, found 228.0474; IR (neat) ν_{max} 3092, 1649, 1606, 1350, 1277, 1152, 1091, 966, 861, 823, 800, 790, 749, 679 cm^{-1}.

3-(Cyclohex-1-en-1-yl)isoquinolin-1(2*H*)-one (3j)

This product was obtained as a yellow solid (207.2 mg, 46% yield); mp = 113–114 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.05 (s, 1H), 8.35 (dm, *J* = 8.0 Hz, 1H), 7.61 (td, *J* = 7.5, 1.3 Hz, 1H), 7.51 (d, *J* = 7.9 Hz, 1H), 7.42 (td, *J* = 7.6, 1.1 Hz, 1H), 6.47–6.49 (m, 2H), 2.40–2.43 (m, 2H), 2.29–2.34 (m, 2H), 1.77–1.83 (m, 2H), 1.66–1.72 (m, 2H). The ^{1}H NMR spectral data are in good agreement with the literature data.[41]

3-Pentylisoquinolin-1(2*H*)-one (3k)

This product was obtained as a white solid (262.7 mg, 61% yield); mp = 111–112 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.24 (s, 1H), 8.11 (d, *J* = 8.0 Hz, 1H), 7.64 (td, *J* = 7.5, 1.3 Hz, 1H), 7.54 (d, *J* = 7.8 Hz, 1H), 7.39 (td, *J* = 7.5, 1.1 Hz, 1H), 6.33 (s, 1H), 2.45–2.47 (m, 2H), 1.62 (p, *J* = 7.4 Hz, 2H), 1.23–1.33 (m, 4H), 0.87 (t, *J* = 6.9 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 162.6, 142.7, 138.3, 132.3, 126.5, 125.7, 125.4, 124.3, 102.1, 32.3, 30.7, 27.7, 21.9, 13.9; HRMS (HESI-ORBITRAP) *m/z* [M + H]$^{+}$ calcd for $(C_{14}H_{18}NO)^{+}$ 216.1383, found 216.1379; IR (neat) ν_{max} 3157,

3093, 3010, 2950, 2926, 2858, 1677, 1640, 1608, 1553, 1476, 1346, 1257, 1174, 992, 886, 755, 727, 619 cm^{-1}.

(*Z*)-3-Hexylideneisoindolin-1-one (5k)

This product was obtained as a beige solid (30.1 mg, 7% yield); mp = 106–107 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.52 (s, 1H), 7.83–7.86 (m, 1H), 7.68 (d, *J* = 7.5 Hz, 1H), 7.61 (t, *J* = 7.5 Hz, 1H), 7.48 (t, *J* = 7.4 Hz, 1H), 5.73 (t, *J* = 8.0 Hz, 1H), 2.32-2.38 (m, 2H), 1.42-1.49 (m, 2H), 1.31–1.33 (m, 4H), 0.87 (t, *J* = 6.7 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ 167.8, 137.4, 133.5, 131.8, 129.4, 128.4, 122.4, 120.0, 108.2, 30.9, 28.8, 26.4, 22.0, 14.0; HRMS (HESI-ORBITRAP) *m/z* $[M + H]^+$ calcd for $(C_{14}H_{18}NO)^+$ 216.1383, found 216.1381; IR (neat) ν_{max} 3180, 3050, 2955, 2923, 2852, 1699, 1463, 1373, 1308, 1147, 1071, 760, 693, 619 cm^{-1}.

3-(tert-Butyl)isoquinolin-1(2*H*)-one (3l)

This product was obtained as a white solid (84.5 mg, 21% yield); mp = 187–188 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.00 (s, 1H), 8.13 (d, *J* = 8.0 Hz, 1H), 7.65 (td, *J* = 7.4, 0.9 Hz, 1H), 7.61 (d, *J* = 7.2 Hz, 1H), 7.41 (td, *J* = 7.3, 1.2 Hz, 1H), 6.38 (d, *J* = 1.2 Hz, 1H), 1.30 (s, 9H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ 162.9, 149.8, 138.0, 132.3, 126.4, 125.7, 124.3, 99.2, 34.3, 28.4 (fewer ^{13}C signals were observed due to signal overlapping); HRMS (HESI-ORBITRAP) *m/z* $[M + H]^+$ calcd for $(C_{13}H_{16}NO)^+$ 202.1226, found 202.1223; IR (neat) ν_{max} 3165, 2957, 1639, 1605, 1557, 1475, 1396, 1366, 1350, 1274, 1248, 1219, 1160, 967, 888, 870, 828, 754, 678 cm^{-1}.

(*Z*)-3-(2,2-Dimethylpropylidene)isoindolin-1-one (5l)

This product was obtained as a brown solid (221.4 mg, 55% yield); mp = 146–147 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.14 (s, 1H), 7.83 (d, *J* = 7.8 Hz, 1H), 7.68 (d, *J* = 7.5 Hz, 1H), 7.61 (td, *J* = 7.7, 1.0 Hz, 1H), 7.48 (td, *J* = 7.4, 0.5 Hz, 1H), 5.77 (s, 1H), 1.24 (s, 9H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ 168.3, 138.8, 132.0, 130.9, 128.5, 128.0, 122.4, 119.8, 117.8, 31.5, 30.4; HRMS (HESI-ORBITRAP) *m/z* $[M + H]^+$ calcd for $(C_{13}H_{16}NO)^+$ 202.1226, found 202.1222; IR (neat) ν_{max} 3071,

2956, 2866, 2297, 1702, 1665, 1612, 1588, 1471, 1399, 1365, 1307, 1290, 1215, 1143, 1092, 1063, 1011, 930, 844, 763, 755, 692 cm^{-1}.

8-Hydroxy-6-methoxy-3-pentylisoquinolin-1(2*H*)-one (3o)

This product was obtained as a yellow solid (203.8 mg, 39% yield); mp = 134–135 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.52 (s, 1H), 10.84 (s, 1H), 6.42 (d, *J* = 2.2 Hz, 1H), 6.38 (d, *J* = 2.2 Hz, 1H), 6.25 (s, 1H), 3.86 (s, 3H), 2.55 (t, *J* = 7.7 Hz, 2H), 1.72 (p, *J* = 7.3 Hz, 2H), 1.36–1.39 (m, 4H), 0.91 (t, *J* = 6.9 Hz, 3H). The 1H NMR spectral data are in good agreement with the literature data.[25]

Isoquinolin-1(2*H*)-one (3m)

A 20 mL glass reaction vial was charged with **1m** (532.0 mg; 2.289 mmol; 1.0 equiv), sodium tetrachloroaurate dihydrate (91.0 mg; 0.229 mmol; 0.1 equiv), silver hexafluoroantimonate (79.0 mg, 0.229 mmol, 0.1 equiv), anhydrous acetonitrile (10 mL) and triflic acid (377.0 mg; 2.515 mmol; 1.1 equiv). The vial was purged with argon and sealed. The reaction mixture was stirred at 85 °C for 6 h. After completion, the reaction mixture was cooled down to room temperature and piperidine (390.0 mg, 4.578 mmol, 2.0 equiv) was added while stirring continued for 30 min. The solvent was removed using a rotary evaporator under reduced pressure (20 mmHg). Ammonium acetate (528.8 mg, 6.867 mmol, 3.0 equiv) and *N*,*N*-dimethylacetamide (5 mL) were added to the reaction vial. The resulting mixture was heated at 120 °C overnight, until the disappearance of the intermediate (**2m**) was observed, as monitored by thin layer chromatography. The reaction mixture was diluted with ethyl acetate (40 mL) and washed with brine (40 mL), and the aqueous phase was extracted with ethyl acetate (2 × 20 mL). The combined organic layers were dried over anhydrous magnesium sulfate, concentrated using a rotary evaporator under reduced pressure (20 mmHg). The resulting residue was purified by flash column chromatography on silica gel (eluent: hexane/ethyl acetate). This product was obtained as a yellow solid (199.4 mg; 60% yield); mp = 214–215 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.24 (s, 1H), 8.17 (d, *J* = 8.0 Hz, 1H), 7.69 (td, *J* = 7.4, 1.2 Hz, 1H), 7.64 (d, *J* = 7.1 Hz, 1H), 7.47 (td, *J* = 7.4, 1.3 Hz, 1H), 7.14–7.18 (m, 1H), 6.54 (d, *J* = 7.11 Hz, 1H). The ^{1}H NMR spectral data are in good agreement with the literature data.[16b]

***tert*-Butyldimethylsilyl 2-((*tert*-butyldimethylsilyl)oxy)-4-methoxybenzoate (7)**

To a flame-dried 100 mL round-bottomed flask was charged with 4-methoxysalicylic acid (**6**, 1.161 g, 6.9 mmol), CH_2Cl_2 (20 mL, anhydrous), DMF (2 mL, anhydrous), Et_3N (3.491 g, 34.5 mmol, 5.0 equiv), *tert*-butyldimethylsilyl chloride (2.607 g, 17.3 mmol, 2.5 equiv), and 4-dimethylaminopyridine (DMAP, 92.8 mg, 0.759 mmol, 0.11 equiv). The mixture was stirred under nitrogen atmosphere at room temperature for 18 h. The reaction mixture was quenched with H_2O (20 mL), and extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with brine (15 mL), dried over anhydrous magnesium sulfate, and concentrated using a rotary evaporator under reduced pressure (20 mmHg). The residue was purified by flash column chromatography on silica gel (eluent: ethyl acetate/hexane), to afford a yellow oil (2.38 g, 87% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.8 Hz, 1H), 6.51 (dd, *J* = 8.8, 2.5 Hz, 1H), 6.39 (d, *J* = 2.4 Hz, 1H), 3.80 (s, 3H), 1.01 (s, 9H), 0.99 (s, 9H), 0.34 (s, 6H), 0.21 (s, 6H). The ^{1}H NMR spectral data are in good agreement with the literature data.[26a]

2-((*tert*-Butyldimethylsilyl)oxy)-*N*,*N*-diethyl-4-methoxybenzamide (8)

To a flame-dried 100 mL round-bottomed flask was charged with *tert*-butyldimethylsilyl 2-((*tert*-butyldimethylsilyl)oxy)-4-methoxybenzoate (**7**, 426.1 mg, 1.074 mmol, 1.0 equiv), CH_2Cl_2 (anhydrous, 20 mL) and DMF (anhydrous, five drops). The reaction mixture was cooled to 0 °C by an ice-water bath. Oxalyl chloride (273.0 mg, 2.148 mmol, 2.0 equiv) was added dropwise to the reaction mixture. The mixture was stirred at 0 °C for 1.5 h. The ice bath was removed and the mixture was further stirred at room temperature overnight. Et_2NH (314.0 mg, 4.297 mmol, 4.0 equiv) was added dropwise to the reaction mixture at room temperature. The reaction was then stirred at room temperature for 5 h, quenched with 100 mL of saturated aqueous NH_4Cl solution, and extracted with CH_2Cl_2 (5 × 10 mL). The combined organic layers were dried over anhydrous magnesium sulfate, and concentrated using a rotary evaporator under reduced pressure (20 mmHg). The residue was purified by flash column chromatography on silica gel (eluent: ethyl acetate/hexane), to afford a colorless oil (334.8 mg, 92% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 (d, *J* = 8.4Hz, 1H), 6.46 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.29 (d, *J*

= 2.4 Hz, 1H), 3.70 (s, 3H), 3.37–3.54 (m, 2H), 3.06–3.19 (m, 2H), 1.16 (t, *J* = 7.2 Hz, 3H), 0.94 (t, *J* = 7.1 Hz, 3H), 0.89 (s, 9H), 0.15 (s, 6H). The ^{1}H NMR spectral data are in good agreement with the literature data.[26a]

2-((*tert*-Butyldimethylsilyl)oxy)-*N*,*N*-diethyl-6-iodo-4-methoxybenzamide (9)

A solution of 2-((*tert*-butyldimethylsilyl)oxy)-*N*,*N*-diethyl-4-methoxybenzamide (**8**, 0.72 g, 2.1 mmol, 1.0 equiv) in anhydrous diethyl ether (30 mL) was cooled to -78 °C. *tert*-Buthyllithium (1.7 *M*, 3.15 mmol, 1.85 mL, 1.5 equiv) was added dropwise, and the reaction mixture was stirred at -78 °C for 2h. Iodine monochloride (0.68 g, 4.2 mmol, 2.0 equiv) was then added dropwise, and the reaction mixture was allowed to gradually warm up to room temperature. After being stirred at room temperature for 3h, the reaction mixture was diluted with diethyl ether (20 mL) and quenched with a saturated aqueous solution of sodium thiosulfate (30 mL) followed by a saturated aqueous solution of sodium bicarbonate (30 mL). The aqueous layer was further extracted with diethyl ether (3 x 15 mL). The combined organic layers were dried over anhydrous magnesium sulfate, and concentrated using a rotary evaporator under reduced pressure (20 mmHg). The residue was purified by flash column chromatography on silica gel (eluent: ethyl acetate/hexane), to afford a beige solid (817.9 mg, 79% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.88 (d, *J* = 2.2 Hz, 1H), 6.28 (d, *J* = 2.3 Hz, 1H), 3.69–3.76 (m, 1H), 3.68 (s, 3H), 3.14–3.23 (m, 1H), 3.03–3.14 (m, 2H), 1.20 (t, *J* = 7.1 Hz, 3H), 1.04 (t, *J* = 7.2 Hz, 3H), 0.88 (s, 9H), 0.18 (s, 3H), 0.14 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 168.0, 160.3, 152.6, 128.2, 116.6, 106.0, 94.0, 55.6, 43.1, 39.3, 25.5, 18.1, 14.0, 12.7, -4.0, -4.7; HRMS (HESI-ORBITRAP) *m/z* $[M + H]^+$ calcd for $(C_{18}H_{31}INO_3Si)^+$ 464.1112, found 464.1107; IR (neat) ν_{max} 2931, 2858, 1633, 1590, 1551, 1461, 1417, 1379, 1362, 1283, 1253, 1207, 1193, 1154, 1138, 1092, 1038, 989, 876, 838, 782, 727 cm^{-1}.

Methyl 2-hydroxy-6-iodo-4-methoxybenzoate (10)

To a stirred solution of 2-((*tert*-butyldimethylsilyl)oxy)-*N*,*N*-diethyl-6-iodo-4-methoxybenzamide (**9**, 1.14 g, 2.5 mmol, 1.0 equiv) in acetonitrile (30 mL) was added Na_2HPO_4 (0.53 g, 3.75 mmol, 1.5 equiv) and trimethyloxonium tetrafluoroborate (1.11 g, 7.5 mmol, 3.0 equiv). After 3h, a saturated aqueous

solution of sodium bicarbonate (15 mL) was added dropwise under vigorous stirring. Additional solid sodium bicarbonate (1.0 g, 11.9 mmol) was added, while stirring was continued. After 18h, water was added (50 mL) and the aqueous layer was extracted with ethyl acetate (3 x 15 mL). The combined organic layers were dried over anhydrous magnesium sulfate, and concentrated using a rotary evaporator under reduced pressure (20 mmHg). The residue was purified by flash column chromatography on silica gel (eluent: ethyl acetate/hexane), to afford a yellow solid (645.7 mg, 84% yield); mp = 118 – 119 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.50 (s, 1H), 7.21 (d, *J* = 2.5 Hz, 1H), 6.45 (d, *J* = 2.5 Hz, 1H), 3.95 (s, 3H), 3.79 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 169.3, 164.7, 164.2, 123.0, 109.3, 101.6, 94.6, 55.8, 51.8; HRMS (HESI-ORBITRAP) *m/z* $[M + H]^+$ calcd for $(C_9H_{10}IO_4)^+$ 308.9618, found 308.9615; IR (neat) ν_{max} 3011, 2953, 1643, 1598, 1557, 1439, 1428, 1325, 1246, 1200, 1186, 1152, 1037, 976, 942, 870, 836, 788, 690 cm^{-1}.

Interconversion experiments

A 20 mL glass reaction vial was charged with 7-methoxy-3-phenyl-1*H*-isochromen-1-one (**2d**, 341.0 mg; 1.352 mmol; 1.0 equiv), ammonium acetate (313.0 mg; 4.055 mmol; 3.0 equiv), *N*,*N*-dimethylacetamide (5 mL). The resulting reaction mixture was heated at 120 °C overnight until the disappearance of the starting material was observed, as monitored by thin layer chromatography. The reaction mixture was diluted with ethyl acetate (40 mL) and washed with brine (40 mL), and the aqueous phase was then extracted with ethyl acetate (2 × 20 mL). The combined organic layers were dried over anhydrous magnesium sulfate, concentrated using a rotary evaporator under reduced pressure (20 mmHg). The resulting residue was purified by flash column chromatography on silica gel (eluent: hexane/ethyl acetate) to afford a white solid (**3d**, 244.6 mg; 72% yield).

A 20 mL glass reaction vial was charged with (*Z*)-3-benzylidene-6-methoxyisobenzofuran-1(3*H*)-one (**4d**, 335.0 mg; 1.328 mmol; 1.0 equiv), ammonium acetate (307.0 mg; 3.984 mmol; 3.0 equiv), *N*,*N*-dimethylacetamide (5 mL). The resulting reaction mixture was heated at 120 °C overnight until the disappearance of the starting material was observed, as monitored by thin layer chromatography. The reaction mixture was diluted with ethyl acetate (40 mL) and washed with brine (40 mL), and the

aqueous phase was then extracted with ethyl acetate (2 × 20 mL). The combined organic layers were dried over anhydrous magnesium sulfate, concentrated using a rotary evaporator under reduced pressure (20 mmHg). The resulting residue was purified by flash column chromatography on silica gel (eluent: hexane/ethyl acetate) to afford a yellow solid (**5d**, 264.0 mg; 79% yield).

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Highlights

- The reaction is mediated by Brønsted acid, and no metal catalyst is required.
- A simple inorganic ammonium salt – NH_4OAc is employed as the nitrogen source in the synthesis of nitrogen containing heterocycles.
- The new method has been successfully employed in the synthesis of a natural product – ruprechstyril.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: