An Efficient and More Sustainable One-Step Continuous-Flow Multicomponent Synthesis Approach to Chromene Derivatives

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A simple and rapid one-step continuous-flow synthesis route has been developed for the preparation of chromene derivatives from the reaction of aromatic aldehydes, α-cyanomethylene compounds, and naphthols. In this contribution, a one-step continuous-flow protocol in a ThalesNano H-Cube Pro™ has been developed for the preparation of these chromene derivatives. This arises from the multicomponent one-step reaction of aromatic aldehydes, α-cyanomethylene compounds, and naphthols. This flow protocol was optimized in 2-methyltetrahydrofuran, which is a more environment-friendly solvent. The faster residence times (<2 min) coupled with elevated pressure (~25 bar) results in an efficient, safer, faster, and modular reaction. Results obtained illustrate that this base-catalyzed reaction affords the respective chromene derivative products in very high yields. The products can then be easily purified by recrystallization, if desired.

Keywords: 2-aminochromenes, arylidenemalononitriles, flow reactor, 1,8-diazabicycloundec-7-ene (DBU), process intensification, Knoevenagel condensation

1. Introduction

The pressing need for greener and efficient organic synthesis is an impetus for a chemist to develop new strategies, tools, and techniques to produce the desired products with minimum expenditure of energy, materials, costs, and labor. Over the past 5 years, the scientific literature has seen an increase in the integration of green chemistry and green engineering principles to arrive at new opportunities to advance the field of green technologies. One such approach is the use of continuous-flow reactors coupled with green organic chemistry approaches to arrive at process intensified reactions. The advent of these continuous-flow technologies into the organic chemistry arena has had a significant impact in improving the efficiency, operability, and sustainability of chemical reactions [1]. By employing this approach of continuous flow, the need for large scale batch reactors and hard to achieve reaction conditions is eliminated, as well as difficult to control reaction parameters. Additional advantages of continuous-flow chemistry include increased mixing efficiency, improved product selectivity and conversions, ability to perform protecting-group free synthesis, application of on-demand (real-time synthesis) and on-site production, and improved worker and operational safety [2]. The continuous-flow processes can be easily optimized due to the flexibility to alter the reaction conditions for each subset of chemicals flowing through the reactor.

Multicomponent reactions (MCRs) have seen a great upsurge in their research investigation, development, and use in the last decade. This is due to MCRs being recognized for their potential in leveraging for new drug and chemical compound discovery. Until the first half of the 20th century, only a few MCRs were known to exist and their importance was scantily realized [3]. For example, the Ugi reaction is a MCR that has garnered much attention due to its significance in the drug discovery arena. In the decades following the discovery of the Ugi reaction, the chemical community has seen the development of a number of Ugi-MCR variants [4]. As new MCR routes are reported over time, new principles, classifications, and strategies have evolved establishing the trend for continuous growth of this novel approach to chemical synthesis [5].

The syntheses of drugs like Crixivan® were achieved easily by using MCR methodology rather than employing a multistep synthesis route, which affords large cost savings [3]. The capacity of MCRs to generate enormous compound libraries, almost to the tune of 10^4, established their vitality in the current synthetic organic chemistry and drug discovery fields. It is clearly established and identified that MCRs can successfully meet the requirements of high throughput compound generation and screening.

In this contribution, a MCR approach was employed for the synthesis of 2-aminochromene derivatives. The chromene derivatives are found in many natural products [6] and have attracted considerable attention as potential agrochemicals, cosmetics, and pigments. Due to their importance, they have also drawn significant attention from organic chemists to develop routes for their synthesis and use in subsequent reactions. An efficient strategy for the direct synthesis of these compounds is the multicomponent reaction of an aldehyde, an α-methylene nitrile, and an activated phenol. Using this direct approach, several homogeneous and heterogeneous catalysts, such as L-proline [7], thiourea dioxide [8], magnesium oxide [9], 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) [10], glycerol [11], and ionic liquids [12] have been explored for the synthesis of these molecules under batch reaction conditions. Recently, guanidine supported on magnetic nanoparticles [13], hydroxyapatites [14], and Amberlyst A21 [15] have also been employed for the synthesis of these molecules in lab-scale batch setup.

Most of the reported methods require prolonged reaction time, reagents in stoichiometric amount, expensive catalysts, tedious and numerous workup steps, toxic solvents or unsustainable reaction media, and/or the generation of low to moderate yields of the desired product. It is not always possible for a geometric scale-up of an optimized lab-scale batch reaction to be realized especially with heat transfer and mixing limitations that may occur upon increasing the scale of the reactor. In batch scale-up, it may also be required to revisit all the conditions and reagents to optimize the reaction. On the other hand, the continuous-flow technology allows efficient control over reaction kinetics enabling high product conversion, desired selectivity and facilitated scale-up provided the same heat and mass transfer, and mixing conditions are maintained.

Keeping in view the advantages associated with continuous-flow reactors, chemical synthesis strategies, and multicomponent reactions, we have reported an efficient, simple, and rapid one-step continuous-flow synthesis approach to 2-aminochromene derivatives. The goal of this contribution is to demonstrate the ability to perform these desired reactions utilizing stoichiometric quantities

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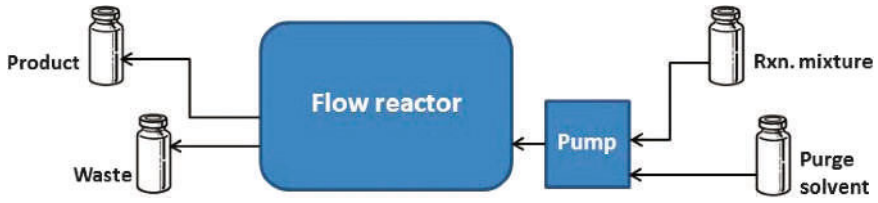


Figure 1. Schematic representation of the flow reactor

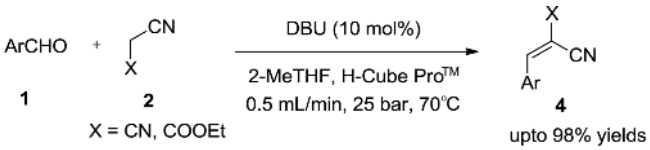
of the reactants, with minimal quantities of base and solvent for the selective and high-level conversion to the desired 2-aminochromene derivatives. This also supports the goal to develop synthesis routes that utilize minimal quantities of solvent or eliminate it entirely. This approach was achieved using a ThalesNano H-Cube Pro™ continuous-flow reactor. The H-Cube Pro™ allows for precise control of temperature and pressure, improves the ease of handling, and also provides increased measures of a safety window. This reactor configuration also allows for faster process optimization and the ability to access new process windows.

The reactor was equipped with a titanium inert catalyst cartridge under elevated pressure and temperature conditions (Figure 1). This reactor configuration can be used with cartridges that are packed with several different types of heterogeneous catalysts for conducting various organic transformations. For this particular contribution, the authors did not have a need for a heterogeneous catalyst. However, in order to use the H-Cube Pro™ flow reactor, the flow path must be outfitted and completed with a catalyst cartridge. We chose to use a cartridge filled with an inert material, titanium, which does not have any mechanistic interference in the reaction progress. The waste stream identified in Figure 1 refers to a purge solvent collection stream. The purge solvent and any undesired fractions of reaction mixture can be collected by switching to the waste stream instead of collecting via the product line.

2. Results and Discussion

2.1. Synthesis of Arylidenemalononitriles. This direct one-step approach to a Knoevenagel condensation of aromatic aldehydes (**1**) and active methylene compounds (**2**) was carried out in a continuous-flow fashion on a ThalesNano H-Cube Pro™ reactor (Scheme 1). This reaction was achieved at a moderate temperature (70 °C) and elevated pressure (25 bar) in the presence of DBU (10 mol%) resulting in the production of arylidenemalononitrile products **4a–j** (Table 1) in excellent yields. DBU is used as a base to abstract the proton from the active methylene compounds facilitating the condensation. The synthesis protocol was optimized by pumping equimolar quantities of an aryl aldehyde and active methylene compound in 2-methyltetrahydrofuran (2-MeTHF) at a flow rate of 0.5 mL/min over an inert titanium catalyst cartridge. The reaction takes place in the heated reaction zone of the H-Cube Pro™ flow reactor, within the catalyst cartridge. The dead volume (as provided by vendor literature) for a 70 mm × 4 mm packed catalyst cartridge is 0.416 mL with a reactant flow rate of 0.5 mL/min yields a calculated residence time of 50 s within the reaction zone. This continuous-flow protocol demonstrates increased significance as the synthesized arylidenemalononitriles can be used in sequential or multicomponent strategies for further ring construction or functional group manipulation.

Scheme 1. Synthesis of arylidenemalononitriles under continuous-flow conditions



2.2. Synthesis of 2-Aminochromenes. The initial attempts for the synthesis of 2-aminochromenes involved the continuous-flow reaction of equimolar solutions of benzaldehyde, malononitrile, and α-naphthol in dichloromethane in the presence of piperidine at room temperature and ambient pressure. This reaction did not afford any of the desired products (Table 2; Reaction 3). However, when the reaction conditions were elevated to 90 °C and a pressure of 50 bar, the reaction afforded a modest 60% yield of desired product (Table 2; Reaction 4) indicating a dependence on temperature and pressure as drivers for an accelerated reaction. Furthermore, the product yield improved significantly when piperidine was replaced with DBU (Table 2; Reaction 5). It is important to note an increase in yield was also achieved as the reaction temperature was lowered to 70 °C and reducing the pressure to 25 bar. DBU was now preferred as a base of choice as it strikingly afforded improved reaction conditions, and the conversion is improved when compared to piperidine. In an effort to further improve and make the reaction conditions greener and more sustainable, other solvents and conditions were explored.

The use of solvent as a reaction medium is inevitable in this reaction methodology as the continuous-flow reactor requires a homogeneous liquid medium to allow for flow through the reactor. This condition needs use of either miscible liquid substrates or dissolution of the solid reaction substrates in a suitable solvent system. Also, the properties of the solvent such as boiling point, vapor pressure, and polarity have to be considered

Table 1. Synthesis of arylidenemalononitriles[a] (Scheme 1)

Entry	Ar	X	Product	Yield[b] (%)	Mp (°C) (Obsd)	Mp (°C) (Lit.)
1	C_6H_5	CN	4a	97	82–84	83–84
2	4-$CH_3OC_6H_4$	CN	4b	96	112–114	114–115
3	3-$NO_2C_6H_4$	CN	4c	97	102–103	104–105
4	4-ClC_6H_4	CN	4d	98	164–166	163–165
5	2-Thienyl	CN	4e	95	88–90	91–92
6	C_6H_5	COOEt	4f	96	46–48	48–49
7	4-$CH_3OC_6H_4$	COOEt	4g	97	80–82	79–81
8	3-$NO_2C_6H_4$	COOEt	4h	98	165–167	166–168
9	4-ClC_6H_4	COOEt	4i	97	87–88	89–90
10	2-Thienyl	COOEt	4j	96	106–108	105–108

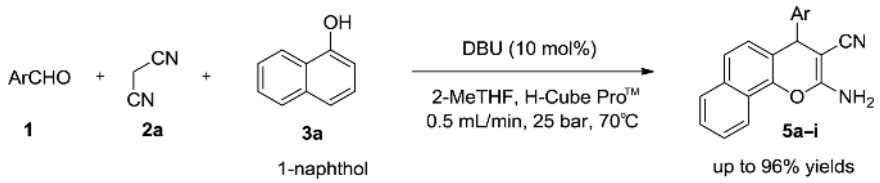
[a] Reaction conditions: a mixture of aryl aldehyde (10 mmol), malononitrile (10 mmol), and DBU (1 mmol) in 2-MeTHF (5 mL) is pumped through H-Cube Pro™ at 0.5 mL/min, 25 bar, and 70 °C using inert titanium catalyst cartridge.
[b] Isolated yields.

Table 2. Optimization of solvent and reaction conditions for the synthesis of 2-aminochromenes

Entry	Solvent	Base	Flow rate (mL/min)	Press. (bar)	Temp. (°C)	Yield (%)
1	PEG 400	DBU	0.5	25	90	NP
2	Aq. PEG 400 (1:1, v/v)	DBU	0.5	25	90	NP
3	CH_2Cl_2	Piperidine	0.5	0	r.t.	NP
4	CH_2Cl_2	Piperidine	0.3	50	90	60
5	CH_2Cl_2	DBU	0.5	25	70	95
6	1-Butanol	DBU	0.3	25	70	18
7	$ClCH_2CH_2Cl$	DBU	0.5	10	90	21
8	Toluene	DBU	0.5	25	90	44
9	CH_3CN	Piperidine	0.5	25	70	10
10	CH_3CN	Piperidine	0.5	50	90	40
11	CH_3CN	DBU	0.5	50	100	55
12	2-MeTHF	DBU	0.5	25	70	96
13	Glycerol	DBU	0.5	10	100	–[a]
14	Ethylene glycol	DBU	0.5	25	100	NP
15	CPME	DBU	0.5	25	100	NP
16	C_2H_5OH	Piperidine	0.3	25	100	10

[a] The reaction mixture could not be pumped due to the high viscosity of glycerol.

Scheme 2. Synthesis of 2-aminochromenes using 1-naphthol under continuous-flow conditions



when using under high pressure and temperature conditions. The sustainability and environmental friendliness of an organic transformation depends, to a large extent, on the reaction solvent used. In view of the above concerns and requirements, a set of solvents was screened for optimizing reaction conditions.

Table 2 shows the representative trials before and after optimization of the reaction protocol with dichloromethane as the solvent. Attempts with alternate solvents such as 1,2-dichloroethane, 1-butanol, ethanol, toluene, acetonitrile, cyclopentyl methyl ether, and ethylene glycol all only furnished low to moderate yields. Subsequent efforts with other solvents such as PEG-400, aqueous mixtures of PEG-400, and glycerol did not afford any of the desired products. However, 2-MeTHF, a biomass-derived solvent, was identified to allow the reaction to proceed to the desired product in very high yields under the optimized conditions. This solvent can be derived from renewable resources and may be a promising alternative to other cyclic solvents like THF. This solvent has also been identified as being an environmentally benign alternative and is a suitable solvent for broad applications in organic chemistry such as organocatalysis, organometallics, and biocatalysis [16].

To demonstrate this approach, Gross and coworkers have also reported [17] a straightforward and interesting procedure for the synthesis of 2-aminochromenes; however, under batch conditions. We believe that this work by Gross et al. along with the current contribution are two successful examples of procedures each with their own merits and benefits. Additionally, the reaction residence time of this contributed flow protocol is 50 s, whereas the room temperature batch protocol described by Gross and coworkers requires between 2 and 4 h of reaction time and 5 mL of solvent per 1 mmol of product. The continuous-flow protocol delivers between 144 and 288 mmol of product during the same 2–4 h of reaction time, and the solvent used per mmol of product is 5× less than that reported by Gross et al. Moreover, the quantity of DBU used in the current flow procedure is 10 mol%. Another important aspect is the safety and scalability of the continuous-flow procedure in contrast to batch reactions. This safety window enhances to a great extent in handling high pressure and temperature reactions as the volume of reaction zone is much smaller in this flow reactor when compared to batch reactors.

Now with the solvent for this 2-aminochromene reaction being optimized (2-MeTHF), further optimization of reaction conditions

Table 3. Synthesis of 2-aminochromenes using 1-naphthol[a] (Scheme 2)

Entry	Ar	Product	Yield[b] (%)	Mp (°C) (Obsd)	Mp (°C) (Lit.) [9, 10, 17, 18]
1	C_6H_5	5a	95	215–217	217–219
2	4-$CH_3OC_6H_4$	5b	93	180–182	182–183
3	4-ClC_6H_4	5c	92	232–233	232–234
4	2-Furanyl	5d	87	171–172	169–172
5	2-Thienyl	5e	91	192–194	193–194
6	4-BrC_6H_4	5f	94	240–242	241–243
7	3-ClC_6H_4	5g	88	229–231	228–230
8	3-$NO_2C_6H_4$	5h	94	214–215	215–216
9	4-$NO_2C_6H_4$	5i	96	236–238	237–238

[a] Reaction conditions: a mixture of aryl aldehyde (10 mmol), malononitrile (10 mmol), 1-naphthol (10 mmol), and DBU (1 mmol) in 2-MeTHF (10 mL) is pumped through H-Cube Pro™ at 0.5 mL/min, 25 bar, and 70 °C using an inert titanium catalyst cartridge.
[b] Isolated yields.

Table 4. Synthesis of 2-aminochromenes using 2-naphthol[a] (Scheme 4)

Entry	Ar	Product	Temp (°C)	Yield[b] (%)	Mp (°C) (Expt.)	Mp (°C) (Lit.) [17, 18b–d]
1	C_6H_5	5j	140	96	278–280	280–282
2	4-$CH_3OC_6H_4$	5k	140	84	193–195	194–196
3	3-$NO_2C_6H_4$	5l	120	92	236–238	239–241
4	4-ClC_6H_4	5m	120	89	207–208	206–208

[a] Reaction conditions: a mixture of aryl aldehyde (10 mmol), malononitrile (10 mmol), 2-naphthol (10 mmol), and DBU (1 mmol) in 2-MeTHF (10 mL) is pumped through H-Cube Pro™ at 0.5 mL/min and 25 bar using an inert titanium catalyst cartridge.
[b] Isolated yields.

was then explored. The reaction conditions with 2-methyltetrahydrofuran and DBU (Schemes 2 and 4) were optimized at 25 bar, 70–140 °C, and a flow rate of 0.5 mL/min.

The synthesis of 2-aminochromenes was achieved by varying the aromatic aldehydes (**1**) employed under the optimized conditions. Both electron-donating and electron-withdrawing aromatic aldehydes afforded the desired products in high yields (Tables 3 and 4). Additionally, all the products in Table 3 (**5a**–**i**) provided excellent yields in all the identified cases (Scheme 2).

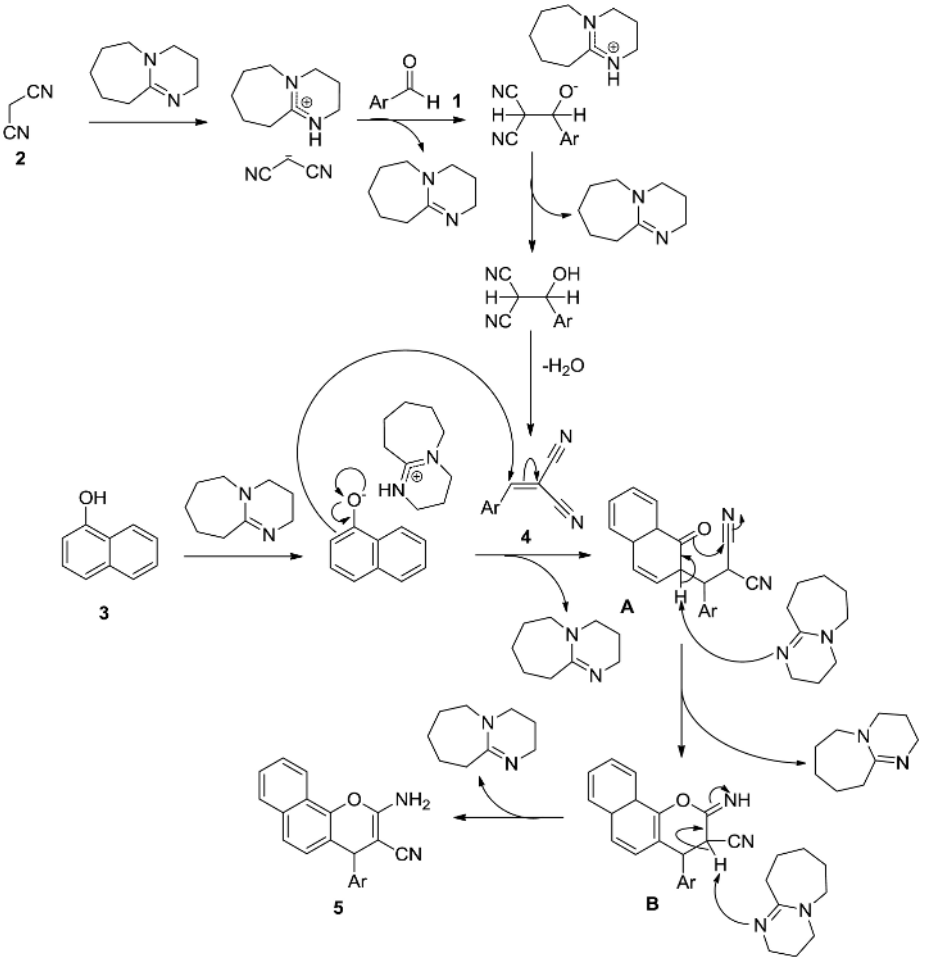
The plausible mechanism (Scheme 3) for this reaction is the initial formation of arylidenemalononitrile (**4**) via the Knoevenagel condensation of the aldehyde with malononitrile resulting in the loss of a water molecule. Further reaction of arylidenemalononitrile (**4**) with naphthol in the presence of base (1,8-diazabicyclo[5.4.0] undec-7-ene; DBU) results in an ortho-substituted C-alkylated product (**A**). This is followed by a subsequent ring closure and rearrangement to afford the desired 2-aminochromene (Scheme 3).

The modularity of the reaction is demonstrated by replacing 1-naphthol with 2-naphthol (Scheme 4; Table 4). These reactions afforded products **5j**–**m** in moderate to high yields at or above 120 °C. The electron-withdrawing and electron-donating contribution from the aromatic aldehydes resulted in relatively less yield of products with the 2-napthol reactant. The overall yields demonstrated for the products are relatively less when compared to those products for the 1-napthol reactant obtained in Table 3. It is demonstrated that the 2-naphthol reaction is found to be less reactive under the given conditions in Table 4 and much less reactive than those obtained for 1-napthol in Table 3. This observed reaction behavior may be attributed to the slightly higher pK_a value for 2-napthol.

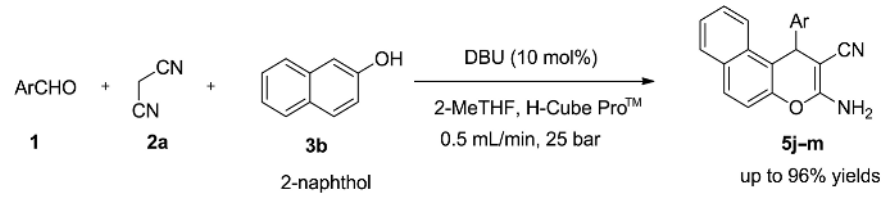
3. Conclusion

In this contribution, the authors have developed and demonstrated a rapid, facile, convenient, and high-yielding continuous-flow protocol for the synthesis of 2-aminochromenes and arylidenemalononitriles. To arrive upon the final set of optimized reaction conditions, this contribution investigated the synthesis of arylidenemalononitriles to demonstrate the feasibility of a multicomponent reaction under continuous-flow conditions. This

Scheme 3. Plausible mechanism for the synthesis of 2-aminochromenes



Scheme 4. Synthesis of 2-aminochromenes using 2-naphthol under continuous-flow conditions



was followed by the initial optimization of temperature and pressure conditions, type of base and its concentration, and then identification (greening) and optimization of the reaction solvent. Next, these optimized conditions and strategy were used, and a level of complexity added by introducing an additional reacting component (1-napthol) to result in the synthesis of 2-aminochromenes also in very high yields. To demonstrate the modularity of this reaction, 2-napthol was used in place of 1-napthol, to also arrive at very good yields.

This methodology for a multicomponent reaction demonstrates the ability to utilize reagents in stoichiometric quantities, at moderate reaction conditions to arrive at the desired products in excellent yields. While it is desired not to utilize a solvent, the reaction does require the use of 2-methyltetrahydrofuran, which is produced from renewable sources, as a mobile phase carrier. To further emphasize the increased sustainability of this reaction, this synthesis utilizes a continuous-flow reactor, which can be easily scaled up for bulk production. Other attractive features include rapid and benign synthesis, ease of handling, modularity, and safety. The resulting arylidenemalononitriles can be directly employed in other sequential flow reactions.

4. Experimental Section

4.1. General. The reagents were obtained commercially and used without further purification. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 300 MHz NMR spectrometer using tetramethylsilane as the internal standard and DMSO-d_6 as the deuterated solvent. Chemical shifts are reported in parts per million (δ) and coupling constants (J) in Hz. Mass spectrometry (MS) data was obtained on Hewlett Packard HP 5973 quadrupole mass selective detector with interface for 6890 series GC with DB-5 column. Melting points were recorded on a Stuart® SMP30 melting point apparatus. Thin-layer chromatography (TLC) was performed on silica gel 60 F254 precoated glass plates.

4.2. Continuous-Flow Synthesis of Arylidenemalononitriles (4a–j). A ThalesNano H-Cube Pro™ flow reactor was equipped with an inert catalyst cartridge packed with titanium (cartridge size: 70 × 4 mm). Prior to the reaction, the hydrogen gas generation was turned off and the reaction line was primed with reaction solvent. The reactor is then programmed to run for 20 min at 70 °C and 25 bar with 12 min solvent post washing. During the 20-minute reaction time, a mixture of aldehyde (**1**) (10 mmol), nitrile (**2**) (10 mmol), and DBU (1 mmol) with 2-methyltetrahydrofuran (10 mL) was pumped through the reactor at a flow rate of 0.5 mL/min. The crude product stream coming out of the exit port was collected. The gas chromatography (GC)–MS spectra of the crude products were recorded. The product may be further used as is or may be purified by recrystallization in ethyl acetate–methanol.

4.3. Continuous-Flow Synthesis of 2-Amino-4-Aryl-4*H*-benzo[*h*]chromene-3-carbonitriles (5a–i). A ThalesNano H-Cube Pro™ flow reactor was equipped with an inert catalyst cartridge packed with titanium (cartridge size: 70 × 4 mm). Prior to the reaction, the hydrogen gas generation was turned off and the reaction line was primed with reaction solvent. The reactor is then programmed to run for 20 min at 70 °C and 25 bar with 12 min solvent post washing. During the 20-minute reaction time, a mixture of aldehyde (**1**) (10 mmol), nitrile (**2**) (10 mmol), 1-naphthol (**3**) (10 mmol), and DBU (1 mmol) with 2-methyltetrahydrofuran (10 mL) was pumped through the reactor at a flow rate of 0.5 mL/min. The crude product stream coming out of the exit port was collected. The GC–MS spectra of the crude products were recorded. Further purification was carried out by recrystallization in ethyl acetate–methanol. Alternatively, purification was also carried out by performing flash column chromatography on a Biotage® SP1 system with SNAP KP-SIL® flash cartridge using ethyl acetate–hexane as the mobile phase.

4.4. Continuous-Flow Synthesis of 3-Amino-1-aryl-1*H*-benzo[*f*]chromene-2-carbonitriles (5j–m). A ThalesNano H-Cube Pro™ flow reactor was equipped with an inert catalyst cartridge packed with titanium (cartridge size: 70 × 4 mm). Prior to the reaction, the hydrogen gas generation was turned off and the reaction line was primed with reaction solvent. The reactor is then programmed to run for 20 min at 120–140 °C and 25 bar with 12 min solvent post washing. During the 20-minute reaction time, a mixture of aldehyde (**1**) (10 mmol), nitrile (**2**) (10 mmol), 2-naphthol (**3**) (10 mmol), and DBU (1 mmol) with 2-methyltetrahydrofuran (10 mL) was pumped through the reactor at a flow rate of 0.5 mL/min. The crude product stream coming out of the exit port was collected. The GC–MS spectra of the crude products were recorded. Further purification was carried out by recrystallization in ethyl acetate–methanol. Alternatively, purification was also carried out by performing flash column chromatography on a Biotage® SP1 system with SNAP KP-SIL® flash cartridge using ethyl acetate–hexane as the mobile phase.

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Conflicts of Interest

The authors declare no competing financial interest.

Supporting Information

Electronic Supplementary Material (ESM) with GC–MS spectra for the representative compounds is available in the online version at doi: 10.1556/1846.2015.00015. This material is available free of charge via the Internet at http://pubs.acs.org.

Abbreviations

DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene
PEG: polyethylene glycol
MCR: multicomponent reaction
2-MeTHF: 2-methyltetrahydrofuran
CPME: cyclopentyl methyl ether
r.t.: room temperature

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