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Flow-Integrated Preparation of Norbornadiene Precursors for Solar Thermal Energy Storage

Nicolò Baggi,[a] Helen Hölzel,*[b] Hannes Schomaker,[c, d] Kevin Moreno,[b] and Kasper Moth-Poulsen*[a, b, c, e]

Molecular solar thermal (MOST) energy storage systems are getting increased attention related to renewable energy storage applications. Particularly, 2,3-difunctionalized norbornadiene-quadricyclane (NBD-QC) switches bearing a nitrile (CN) group as one of the two substituents are investigated as promising MOST candidates thanks to their high energy storage densities and their red-shifted absorbance. Moreover, such NBD systems can be prepared in large quantities (a requirement for MOST-device applications) in flow through Diels-Alder reaction between cyclopentadiene and appropriately functionalized propynenitriles. However, these acetylene precursors are traditionally prepared in batch from their corresponding acetophenones using reactive chemicals potentially leading to health and physical hazards, especially when working on a several-grams scale. Here, we develop a multistep flow-chemistry route to enhance the production of these crucial precursors. Furthermore, we assess the atom economy (AE) and the E-factor showing improved green metrics compared to classical batch methods. Our results pave the way for a complete flow synthesis of NBDs with a positive impact on green chemistry aspects.

Introduction

The development of efficient and scalable renewable energy storage concepts is a key objective of our world society.[1] This goal has led to a growing interest in molecular photoswitches capable of absorbing light and storing a fraction of it as energy – the so-called molecular solar thermal (MOST) energy storage systems.[2–7] Several molecular photoswitches are being explored for MOST applications, including azobenzenes,[8] dihydroazulenes-vinylheptafulvenes,[9,10] and norbornadiene-quadricyclane (NBD-QC) systems.[11,12]

These latter switches are particularly appealing due to their high energy storage density (up to 1 MJ/kg) and the attractive, photophysical properties achieved through the introduction of donor (D) and acceptor (A) groups.[13] 2,3-D-A-norbornadienes can be prepared through Diels-Alder reaction between cyclopentadiene and appropriately functionalized acetylenes as dienophiles, a synthetic route that can be also performed in flow to achieve a rapid and scalable synthesis.[14] Alternatively, similarly designed switches can be synthesized through Pd-catalyzed cross-coupling reaction on 2-bromo-3-cyano-norbornadiene (Figure 1).[15]

As the large-scale synthesis of 2,3-D-A-norbornadienes through a Diels-Alder reaction in flow is established,[14] a current challenge is thus to develop efficient, scalable, and as sustainable as possible chemistry routes for the required dienophile precursors, such as propynenitriles. These valuable molecules can be prepared from their corresponding acetophenones,[16] derivatives that can also be obtained from bio-based renewable sources such as lignin,[17–19] thus comply-

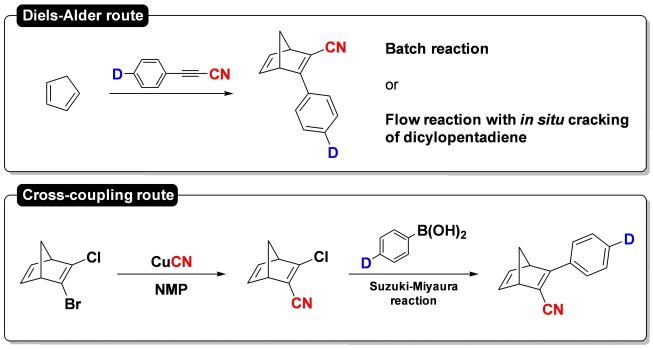

Figure 1. Alternative synthetic routes towards 2,3-D-CN-norbornadienes, D = Donor.

[a] *Dr. N. Baggi, Prof. Dr. K. Moth-Poulsen*
The Institute of Materials Science of Barcelona, ICMAB-CSIC
Bellaterra, 08193 Barcelona (Spain)
E-mail: kasper.moth-poulsen@upc.edu

[b] *Dr. H. Hölzel, Dr. K. Moreno, Prof. Dr. K. Moth-Poulsen*
Department of Chemical Engineering
Universitat Politècnica de Catalunya, EEBE
Eduard Maristany 10–14, 08019 Barcelona (Spain)
E-mail: helen.holzel@upc.edu

[c] *H. Schomaker, Prof. Dr. K. Moth-Poulsen*
Department of Chemistry and Chemical Engineering
Chalmers University of Technology
SE-412 96 Gothenburg (Sweden)

[d] *H. Schomaker*
AutoSyn AB
Plockerotegatan 207, SE-422 57 Hisings Backa (Sweden)

[e] *Prof. Dr. K. Moth-Poulsen*
Catalan Institution for Research & Advanced Studies, ICREA
Pg. Lluís Companys 23, 08010 Barcelona (Spain)

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ing with *principle 7* of the "Green ChemisTREE".[20] Alternative synthetic approaches towards propynenitriles include the introduction of the nitrile group in terminal acetylenes,[21–24] the conversion of other functional groups (e.g. –OH, –CHO, etc.)[25,26] to CN or their synthesis from oxopropanoates by reaction with lithium bis(trimethylsilyl)amide (LiHMDS) and diethyl chlorophosphite.[27]

Herein, we present a multistep, integrated flow and batch process to convert 4′-substituted acetophenones into a series of application-relevant alkynes (Scheme 1).

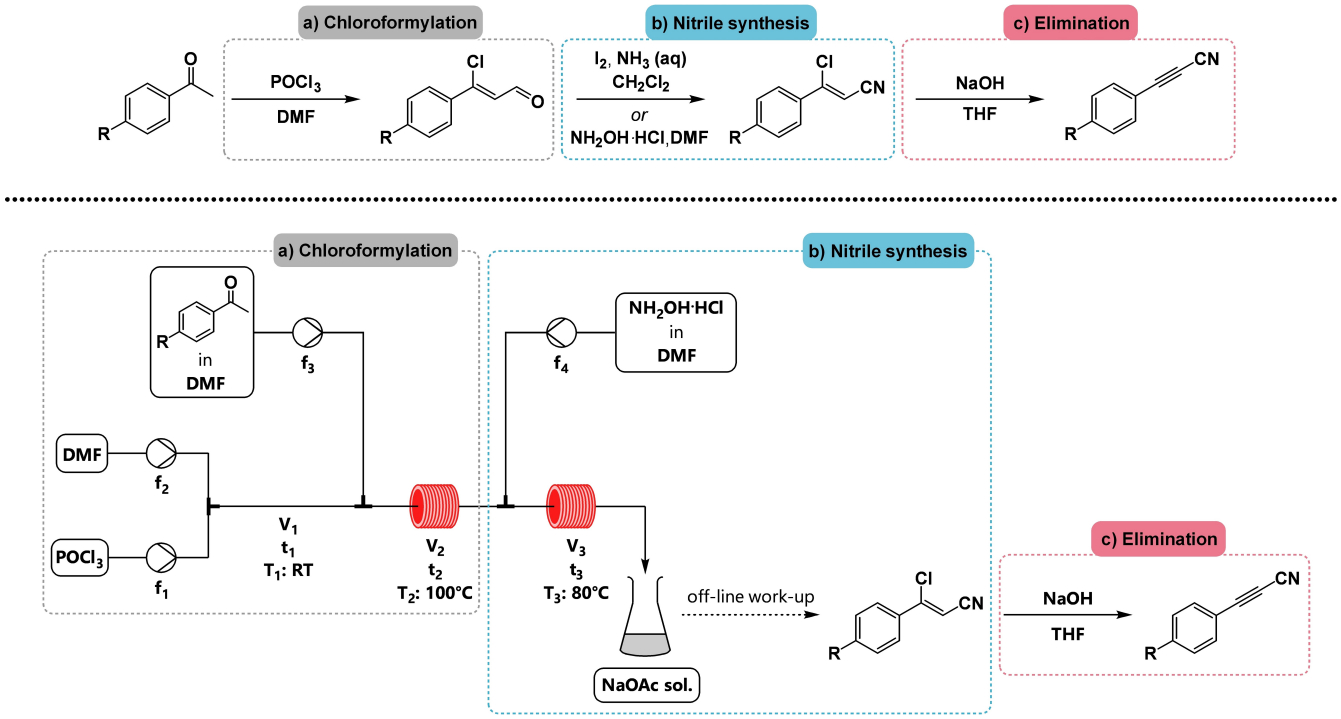
We show the versatility of the method by applying it to four commercially available starting materials. Further, we illustrate and verify the adaptability of the process by performing a scaled-up reaction of a selected compound. Moreover, we assess the atom economy (AE)[28] and the E-factor[29] of this flow-integrated route, to compare them to those of the previously reported batch-based procedures and discuss prospects for future improvement.

The choice of integrating flow technology is motivated both by the need for scalable production of MOST precursors (a crucial requirement for their final application) and by the fact that it represents a greener and more sustainable synthetic alternative to classical batch processes.[30–32] Furthermore, it allows not only to achieve improved mass transfer and one-flow multi-step syntheses but also to handle reactive and toxic starting materials and/or intermediates more safely, owing to a more efficient heat transfer.[33,34]

This latter point is of particular interest, considering the chemicals used to convert acetophenone derivatives into propynenitriles (Scheme 1). For instance, the first step consists of a chloroformylation (Scheme 1, step **a**), a reaction in which the Vilsmeier reagent (VR) allows the conversion of a ketone to a β-chloroenal. As it involves dimethylformamide (DMF, substance of very high concern, SVHC) and $POCl_3$ (corrosive chemical affording hydrochloric and phosphoric acid upon hydrolysis), and the reaction of these two chemicals leading to the formation of the VR, whose decomposition might lead to a thermal runaway,[35] is highly exothermic, flow chemistry guarantees to operate in safer conditions, especially when working on a large scale.

Indeed, some examples of continuous-flow chloroformylation Vilsmeier-Haack reactions are already available in the literature: Buchwald and Pellegatti described the conversion of three acetophenone derivatives and three acetyl heterocycles to their respective β-chloroacroleins[36] while Stevens and co-workers showed that DMF can be replaced by the more expensive, but more environmentally friendly, DEF (N,N-diethylformamide) or N-formylmorpholine in the chloroformylation of cyclohexanone.[37]

After the chloroformylation, the β-chloro-cinnamonitrile is obtained as an intermediate species (Scheme 1, step **b**) by using hydroxylamine hydrochloride[38] or I_2 and aqueous ammonia in dichloromethane, as reported by Sharma *et al.*[16] Finally, the elimination of the chlorine with aqueous NaOH in THF affords the target molecule (Scheme 1, step **c**).[16]



Scheme 1. (top) Traditional batch route to synthesize propynenitriles from the corresponding acetophenones, showing the 3 involved steps: **a**) Chloroformylation, **b**) Nitrile synthesis, and **c**) Elimination reaction. (bottom) Flow-integrated multistep synthesis route presented in this work, where f: flow rates, V: reactors, t: residence times, and T: temperatures. V_2 and V_3 (red coils) are heated reactors. **DMF**: dimethylformamide; **$POCl_3$**: phosphorus(V) oxychloride; **$NH_2OH{\cdot}HCl$**: hydroxylamine hydrochloride; **NaOAc**: sodium acetate; **THF**: tetrahydrofuran.

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Results and Discussion

In the development of the flow-integrated route to prepare propynenitriles (Scheme 1, bottom), step **a** is carried out with the same reagents used in the batch synthesis. Meanwhile, I_2 and aqueous ammonia in dichloromethane are not used in step **b**, as they might affect the performances of the flow setup during the use, being a slurry and not a solution.

The potential hazard of hydroxylamine is reduced by handling the salt ($NH_2OH{\cdot}HCl$),[36] and the use of a flow setup further limits the risks of exposure to the chemical. Moreover, thanks to these choices, the involved steps can be telescoped in a single flow reaction sequence (Scheme 1, bottom, step **a** + step **b**), thus avoiding a solvent switch and an increase of the required chemicals to obtain the same chloropropenenitrile species.

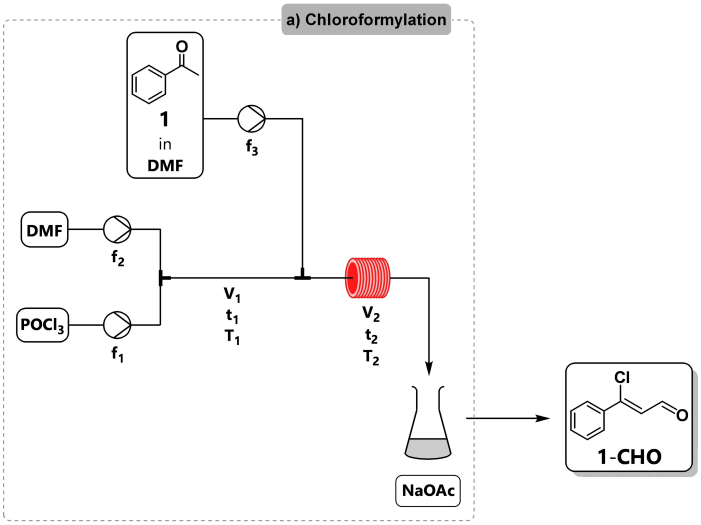
Aiming to reduce the amount of used DMF and considering its possible decomposition in the presence of the NaOH aqueous solution needed to carry out the last elimination step,[39] we decided to keep performing step **c** of the synthesis of the target dienophile precursors of norbornadiene MOST systems in batch, in THF (Scheme 1).

Our multistep process was built step-by-step, starting with the optimization of the chloroformylation reaction (Scheme 1, bottom, step **a**). Acetophenone (**1**) was selected to optimize the reaction conditions. The investigated reaction conditions are listed in Table 1.

The reaction was performed on a 1 M solution of **1** in DMF with neat $POCl_3$ (10.69 M) and DMF (12.97 M) as reagents for the formation of the Vilsmeier reagent (VR) inside the first reactor (V_1). 2.2 eq of $POCl_3$ and 3.3 eq of DMF were used during the different experiments, as reported by Pellegatti and Buchwald for the chloroformylation of the same substrate.[36] The reactions per experimental conditions were carried out through partial injections of $POCl_3$ and **1** from 5 mL sample loops, SLs (injected volume of $POCl_3$: 338 µL/run, injected volume of **1**: 1644 µL/run). A residence time of 2 min for the preparation of this species at room temperature was selected following reported values in the literature.[36,40] A second reactor (V_2) of 4 mL was used for the reaction between the generated VR and **1** while varying the temperature (T_2) and the residence time (t_2). The outlet stream of this second reactor was collected in vials containing a saturated sodium acetate solution, so to obtain the target 3-chloro-3-phenylacrylaldehyde (**1-CHO**) by hydrolysis. Details on the flow setup are available in the Experimental Section and the ESI (Figure S1).

Starting with a residence time of 10 min at 60 °C (entry 1, Figure S3), a conversion close to 40% was achieved. An improvement was observed by increasing the reactor temperature to 80 °C while keeping the same residence time (entry 2, Figure S4). Further rising T_2 to 100 °C led to a conversion of 74% (entry 3, Figure S5). As doubling the residence time in V_1 and V_2 while setting T_2 at 80 °C resulted in a conversion of 71% (entry 4, Figure S6), we set the experimental conditions of "entry 3" as the first building block of the overall synthetic route. The conditions were also tested in another commercially available flow setup with little changes to account for the technologies being different (Details in the Experimental

Table 1. Optimization of the flow reaction conditions for the chloroformylation (step **a**) of acetophenone (**1**), where f: flow rates, V: reactors, t: residence times, and T: temperatures.



Entry[a]	f_1 [µL/min]	f_2 [µL/min]	f_3 [µL/min]	T_1 [°C]	t_1 [min]	T_2 [°C]	t_2 [min]	Conv.[b] [%]
1	56	70	274	RT	2	60	10	37
2	56	70	274	RT	2	80	10	61
3	56	70	274	RT	2	100	10	74
4	28	35	137	RT	4	80	20	71

[a] Fixed parameters: Conc. of **1**: 1 M; V_1: 252 µL; V_2: 4 mL; P: 3 bar. [b] Evaluated by ^{1}H-NMR of the crude product.

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Section and the ESI, Figure S2). Again, the outlet stream was collected and quenched. Consistent results were achieved (i.e., 77% conversion to 3-chloro-3-phenylacrylaldehyde, **1-CHO**) according to the ^{1}H-NMR of the crude product (Figure S7), thus showing the reproducibility of the reaction on two different flow setups available in the market. The same results were also obtained when the pressure of the system was set to 6 bar through a back-pressure regulator unit, showing that the system pressure has no influence on the reaction.

Before moving to step **b** of the synthetic route (i.e., the generation of the 3-chloropropenenitriles), we decided to broaden the scope of our investigation and we tested the optimized conditions on other functionalized acetophenones (Figure 2).

Specifically, 4′-methoxyacetophenone (**2**) is the starting material for one of the most used donor-acceptor NBDs for solar thermal energy storage,[41,42] 4′-(methylthio)acetophenone (**3**) is a substrate that was never tested before to prepare the corresponding propynenitrile and 4′-dimethylaminoacetophenone (**4**) is of particular interest as it bears a very strong electron-donating substituent and the obtainable target nitrile can be used to synthesize a red-shifted NBD (λ_{max} = 374 nm; λ_{onset} = 427 nm).[43]

Compared to the results on **1**, the procedure led to even better conversions in the presence of the 4′-substituents. Indeed, 94%, quantitative and quantitative conversions were determined for 4′-methoxyacetophenone (**2**), 4′-(methylthio)acetophenone (**3**), and 4′-dimethylaminoacetophenone (**4**), respectively (Figures S8–S10).

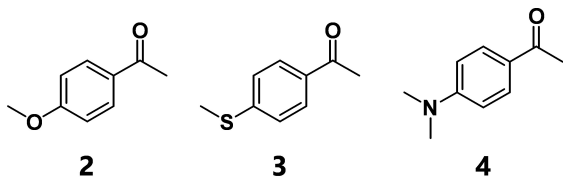

Figure 2. Investigated 4′-substituted acetophenones.

Encouraged by these results, we have modified the flow setup (Figure 3) to add a fourth pump and a third reactor (V_3) for the reaction with $NH_2OH \cdot HCl$ in DMF (step **b**). We decided to test the telescoped reactions on **1** by using 1.2 eq of hydroxylamine hydrochloride (1.20 M in DMF). A residence time of 6 min was chosen and the temperature of V_3 was set to 80 °C.

As the ^{1}H-NMR of the crude product (Figure S11) showed the presence of 3-chloro-3-phenylacrylonitrile (**1-CN**) and no peaks related to 3-chloro-3-phenylacrylaldehyde (**1-CHO**), these conditions were considered as suitable to perform the reaction also on ketones **2**, **3** and **4**. Again, high conversions of the acetophenone-based substrates to the respective 3-chloropropenenitriles (i.e., **2-CN**, **3-CN**, and **4-CN**) were determined by ^{1}H-NMR of the crude products (95%, 74%, and quantitative, respectively, Figures S12–S14).

At this point, workups of the collected solutions were performed off-line to isolate the target products in moderate yields over the two steps: 30% for **1-CN**; 38% for **2-CN**; 30% for **3-CN**; 45% for **4-CN**. While extraction followed by column chromatography was carried out to isolate **1-CN**, **2-CN**, and **3-CN**, a filtration allowed to isolate **4-CN** as it precipitated in the saturated sodium acetate solution. The ^{1}H-NMR of the crude product (Figure S14) revealed the presence of the target compound as the main component (>80%) of the crude product. The possibility of isolating the nitrile species in this way is noteworthy as it allows to easily remove DMF through washings with H_2O and doesn't require the use of organic solvents for extraction and purification by chromatography.

Concerning the achieved overall isolated yields, it must be highlighted that, generally, around 1.5-reactor-volume amounts of material are needed to reach steady-state conditions for homogeneous liquid systems.[44] As all the presented optimization reactions were carried out using sample loops and the used volumes of reactants solutions per run were below the reactor volumes, it should be considered that the reported

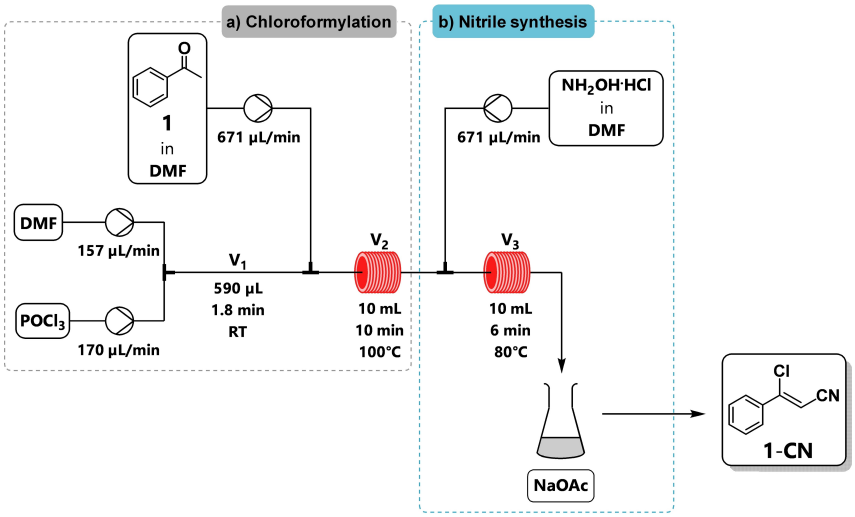

Figure 3. Upgraded flow setup for the telescoped synthesis (step **a** + step **b**) of 3-chloro-3-phenylacrylonitrile (**1-CN**) from acetophenone (**1**) where V_1, V_2 and V_3 indicate the three reactors.

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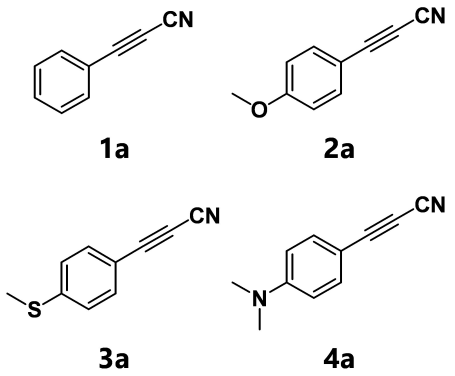


Figure 4. Synthesized alkyne precursors for NBD-based MOST systems.

overall yields could be influenced by the non-steady-state operative conditions. Indeed, by performing the experiment on a 5-fold larger scale (Details in the Experimental Section and the "Synthetic procedures" section of the SI), the isolated yields of the reactions to convert acetophenones **1**–**4** to chloropropenenitriles **1**-**CN** – **4**-**CN** were increased (**1** to **1**-**CN**: 49%; **2** to **2**-**CN**: 45%; **3** to **3**-**CN**: 40%; **4** to **4**-**CN**: 52%). Moreover, while extraction followed by purification by column chromatography was still necessary to obtain **1**-**CN**, not only **4**-**CN**, but also **2**-**CN** and **3**-**CN** could be isolated by filtration (**2**-**CN**: 88% ca. pure; **3**-**CN**: 76% ca. pure; **4**-**CN**: 80% ca. pure. ^{1}H-NMRs are provided in the "Synthetic procedures" section of the SI) as they precipitated in the saturated sodium acetate solution. The resulting throughputs are 1.3 g/h (**1**-**CN**), 1.4 g/h (**2**-**CN**), 1.4 g/h (**3**-**CN**) and 1.7 g/h (**4**-**CN**). As the purity of these intermediates does not influence the last step ("Synthetic procedures" section of the SI) and degradation might occur when attempting to do chromatography, crude chloropropenenitriles can be directly converted to the corresponding alkynes (Figure 4) in THF with an aqueous solution of NaOH (Scheme 1, step **c**). The target dienophiles can be obtained in high yields after purification, if necessary (see the Experimental Section and the ESI for details).

Considering the need for large amounts of propynenitriles precursors to synthesize 2,3-D-CN-norbornadienes for the target MOST energy storage application, the larger scale flow reaction was carried out over 9 h as proof of principle of the utility of this flow-integrated method and 12.6 g of **2**-**CN** were produced ("Up-scaled synthesis of **2**-**CN**" section in the ESI, Figure S15).

Additionally, to evaluate if the elimination reaction could have been possibly done in DMF, thus telescoping the whole synthetic process in flow, a test on **2**-**CN** was carried out in batch and it afforded **2a** in 31% yield after purification (compared to 94% in THF). Replacement of the aqueous alkaline solution with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as base showed no formation of the target alkyne. Details are provided in the "Additional batch syntheses tests" section of the ESI (Figure S16–S17).

Green Chemistry Metrics

In addition to the high throughput of this flow-integrated synthetic approach to afford propynenitriles, it is worth recalling that this strategy is operationally safer than the batch method.

Furthermore, by comparing the flow-integrated route to obtain alkyne **4a** from 4′-dimethylaminoacetophenone (**4**) to the batch synthetic route described in the literature (Scheme 2),[43] an improvement not only in the production rate but also in sustainability is observed. First, the atom economy [Eq. (1)], AE, of the overall process is increased from 20.8% to 34.1% ("Details on Green Metrics assessment" section in the SI) by telescoping the first two steps in the flow setup.

$$AE = \frac{MW_{product}}{\sum MW_{reactants}} \cdot 100 \quad (1)$$

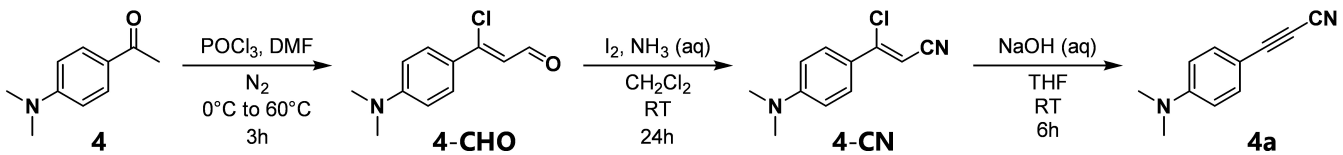
Secondly, we decided to determine the environmental factor [Eq. (2)], E-factor ("Details on Green Metrics assessment" section in the SI), to quickly estimate the sustainability of the two routes to afford the same propynenitrile **4a** and show the improvement provided by the integration of flow chemistry.

$$\text{E-factor} = \frac{m_{waste}}{m_{product}} = \frac{(m_{raw\ materials} - m_{product}) + m_{solvents}}{m_{product}} \quad (2)$$

By switching from the full batch route to the flow-integrated one, the E-factor decreased by a factor of ~2 (509 vs. 226) or ~3.5 (502 vs. 143) depending on whether H_2O was included or not, as it is known to lead to misrepresenting E-factors.[45]

Furthermore, if we consider the overall route towards the 2,3-D,CN-NBDs (i.e. flow-integrated preparation of the propynenitriles + Diels-Alder reaction in batch or in flow) and we compare it to the alternative cross-coupling route, the improvement in sustainability is even more evident:

1. The nitrile group can be introduced by avoiding the use of a reprotoxic solvent such as N-methyl-2-pyrrolidone (NMP) and cyanide salts (CuCN, NaCN).
2. The final photoswitches can be obtained without requiring palladium catalysts, phosphines, bases, and operative inert conditions.



Scheme 2. Full batch synthetic route to prepare **4a** from 4′-dimethylaminoacetophenone (**4**).[43]

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Conclusions

In conclusion, we have proposed a flow-integrated route to convert four acetophenone-based derivatives to their corresponding propynenitriles, precursors in the synthesis of norbornadiene (NBD) photoswitches used for solar thermal energy storage. In addition to the safer operative conditions guaranteed by using flow chemistry setups, the route that we described allowed us to prepare an application-relevant NBD starting material in an up-scaled way, using readily available starting materials such as e.g., 4′-methoxyacetophenone. Additionally, the integration of flow technologies and the telescoping of two of the three reaction steps led to an improvement in sustainability, as indicated by the improved atom economy (AE) and E-factor compared to the traditional batch route. Our work illustrates a more sustainable and scalable complete flow synthesis of NBDs, where the preparation of functionalized acetylenes can be used to produce feedstocks to the previously described large-scale Diels-Alder reaction in flow.[14]

For future, larger scale implementation in molecular solar thermal energy storage technology, we note that many acetophenone derivatives are available through lignin-based sources,[17–19] thus paving the way for new and sustainable biocarbon based solar energy storage technologies.

Experimental Section

Flow setups

a) Syrris ASIA system integrated with a Gilson 403B collection module and manual injection port via Knauer multiposition valve.

The ASIA pump units are based on highly chemically resistant syringe pumps. A Syrris ASIA Pressure Controller was used to maintain the pressure of the system at 3 bar during the reactions. Standard ETFE (Ethylene tetrafluoroethylene) tubing with an inner diameter of 0.030'' (0.762 mm) and $^1/_4$"-28 UNF flat bottom fittings with PPS (Polyphenylene Sulfide) nuts and ETFE ferrules were used for the connections to the reactors and pumps. An ASIA PFA (Perfluoroalkoxy) tube reactor (inner diameter of 0.5 mm, 4 mL, operative T: ambient to 125 °C) from Syrris was used for the heated reaction. Reagents were injected from 5 mL PTFE (Polytetrafluoroethylene) sample loops.

b) Vapourtec R4/R2C + /R2S + system integrated with an autosampling and collection module.

The R2C + unit is based on acid-compatible piston pumps. The R2S + module is instead based on acid-resistant V-3 peristaltic pumps. An acid-resistant, passive, spring-loaded back-pressure regulator provided by Vapourtec was used to maintain the pressure of the system at 3 (or 6) bar during the reactions. Standard PFA tubing with an inner diameter of 1 mm and either $^1/_4$"-28 PFA nuts and adaptors were used for the connections to the reactors and pumps. Two PFA tube reactors (inner diameter/internal bore of 1 mm, 10 mL, operative T: ambient to 150 °C) from Vapourtec were used for the heated reactions. Reagents were injected from 2 mL and 0.5 mL PFA sample loops. Larger scale reactions were carried out using in-house assembled 10 mL and 2.5 mL ETFE sample loops with an inner diameter/internal bore of 1 mm. ETFE tubing was purchased from IDEX.

General procedures for the optimization reactions in flow

Flow setup **a** (Syrris): V_1: 228 μL; V_2: 4 mL.

338 μL of neat $POCl_3$ (10.69 M, 2.2 eq) was injected from a 5 mL sample loop at a flow rate of 57 μL/min and combined with a continuous stream of DMF (12.97 M, 3.3 eq based on $POCl_3$ injection) at 70 μL/min at a T-mixer to generate the Vilsmeier reagent in V_1 at RT (t_1: 1.8 min). 1.644 mL of acetophenone (**1**) in DMF (1 M, 1 eq) was injected from a 5 mL SL at 274 μL/min and combined with the outflow of V_1 at a T-mixer so that the streams could react in V_2 at 100 °C (t_2: 10 min).

To obtain the corresponding β-chloroenal: the outlet stream from V_2 was collected via the automated collector in a vial containing a saturated sodium acetate solution to quench the reaction and obtain the target product by hydrolysis.

Flow setup **b** (Vapourtec): V_1: 590 μL; V_2: 10 mL; V_3: 10 mL.

A syringe pump integrated in the autosampling module filled the sample loops with the reagents solutions by pushing them with CH_3CN. 0.5 mL of neat $POCl_3$ (10.69 M, 2.5 eq) and 0.5 mL of DMF (12.97 M, 3.3 eq) were injected from two 0.5 mL sample loops at 170 μL/min and 157 μL/min, respectively, to meet at a T-mixer and then generate the Vilsmeier reagent in V_1 at RT (t_1: 1.8 min). 2 mL of acetophenone-based substrate in DMF (1 M, 1 eq) was injected from a 2 mL SL at 671 μL/min so that the streams could meet at a T-mixer and react in V_2 at 100 °C (t_2: 10 min).

To obtain the corresponding β-chloroenal: the outlet stream from V_2 was collected in a vial containing a saturated sodium acetate solution to quench the reaction and obtain the target product by hydrolysis.

To obtain the corresponding β-chloropropenenitrile: 2 mL of hydroxylamine hydrochloride in DMF (1.20 M, 1.2 eq) were injected from a 2 mL SL at 671 μL/min to mix with the stream coming from V_2 at a T-mixer and react in V_3 at 80 °C (t_2: 6 min). The outlet stream from V_3 was collected in a vial containing a saturated sodium acetate solution to quench the reaction.

General procedure for the 5-fold scaled-up reaction in flow

Flow setup **b** (Vapourtec): V_1: 590 μL; V_2: 10 mL; V_3: 10 mL.

A syringe pump integrated in the autosampling module filled the 2.5 mL sample loops with DMF and $POCl_3$ by pushing them with CH_3CN. The 10 mL sample loops used for the acetophenone-based substrate and hydroxylamine hydrochloride were filled manually. 2.5 mL of neat $POCl_3$ (10.69 M, 2.5 eq) and 2.5 mL of DMF (12.97 M, 3.3 eq) were injected from two 2.5 mL sample loops at 170 μL/min and 157 μL/min, respectively, to meet at a T-mixer and then generate the Vilsmeier reagent in V_1 at RT (t_1: 1.8 min). 10 mL of acetophenone-based substrate in DMF (1 M, 1 eq) was injected from a 10 mL SL at 671 μL/min so that the streams could meet at a T-mixer and react in V_2 at 100 °C (t_2: 10 min).

To obtain the corresponding β-chloropropenenitrile: 10 mL of hydroxylamine hydrochloride in DMF (1.20 M, 1.2 eq) were injected from a 10 mL SL at 671 μL/min to mix with the stream coming from V_2 at a T-mixer and react in V_3 at 80 °C (t2: 6 min). The outlet stream from V3 was collected in a flask containing a saturated sodium acetate solution to quench the reaction.

General method for the elimination reaction in batch

In a typical procedure, the β-chloropropenenitrile substrate (1 eq) was dissolved in THF, and aqueous NaOH (2.5 eq) was added to the

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obtained solution. Upon completion of the reaction (monitored by thin-layer chromatography), water was added. If precipitation occurred, the target alkyne was isolated by filtration, otherwise AcOEt would be used for extraction. In that case, the combined organic phases were dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated under vacuum affording the target propynenitrile. Detailed procedures and full characterizations (^{1}H- and ^{13}C-NMR spectra, high-resolution mass analyses, and melting points) are provided in the ESI.

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Conflict of Interests

Hannes Schomaker is active in the company AutoSyn AB, working with flow chemistry methods.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Energy Storage · Flow Chemistry · Multistep Reactions · Norbornadiene · Propynenitrile

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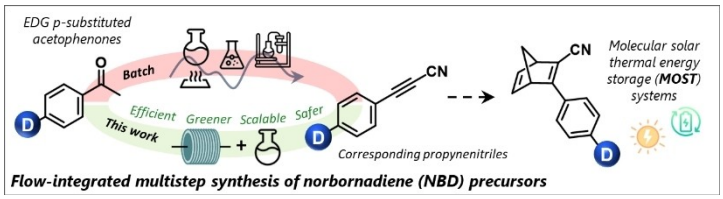

Flow-integrated multistep synthesis of norbornadiene (NBD) precursors

The application of norbornadienes (NBDs) in Molecular Solar Thermal (MOST) energy storage devices requires the availability of precursors such as propynenitriles in large quantities. The integration of flow chemistry technologies leads to a scalable, more sustainable, and safer multistep route for the synthesis of these dienophiles from acetophenones than the traditional full batch method.

Dr. N. Baggi, Dr. H. Hölzel, H. Schomaker, Dr. K. Moreno, Prof. Dr. K. Moth-Poulsen**

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Flow-Integrated Preparation of Norbornadiene Precursors for Solar Thermal Energy Storage

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