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Revitalised Hofmann carbylamine synthesis made possible with flow chemistry

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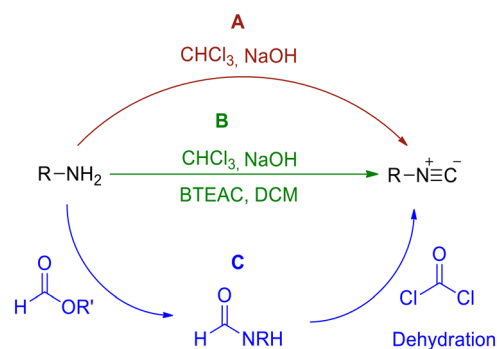
Isocyanides are of relevance to several scientific fields; however, over the last 150 years only a limited number of synthetic strategies have been reported for preparing them. In a newly developed flow approach, a neglected method for preparing isocyanides, the Hofmann carbylamine reaction, has been revisited and revitalised. The approach developed afforded the preparation of a diverse library of isocyanides in good conversions while only requiring a 15 min residence time at 70 °C. In addition, the method is operationally easy to apply, and it affords several advantages over the more commonly employed strategy of preparing isocyanides which involves the conversion of amines to formamides followed by dehydration to an isocyanide.

Isocyanides, commonly referred to as isonitriles or carbylamines, are organic functional groups with the general form R–NC, where an aryl/alkyl group is sigma bonded to a cyanide group through the nitrogen atom which is positively charged. Isocyanides exhibit reaction plasticity, being able to contribute just a few atoms or play a vital role in large multi-molecular assemblies.² These compounds are synthetically more challenging to access than conventional cyanides (R–CN) and notably, are characterised by an overpowering pungent odour which is particularly prevalent in low molecular weight examples. They are generally considered to not exhibit acute toxicity, but caution should be taken when handling them, as toxicity studies still remain limited.³

Since their discovery more than a century and a half ago,⁴ they have been shown to have relevance in multiple disciplines of science including astronomy, biology, chemistry, information technology, and materials science.^{2,5–7} Within the context of organic chemistry, isocyanides have gained attention in heterocyclic syntheses as well as multi-component reactions, such as the Ugi and Passerini reactions.^{1,2} The Ugi reaction in particular has gained recognition as a greener method for preparing molecular assemblies, achieving utility in the drug discovery space.⁸

Lieke, in 1859, reported the first synthesis of an isocyanide by reacting silver cyanide with allyl iodide, followed by treatment with potassium cyanide.⁹ Thereafter, in 1867, the Hofmann carbylamine synthesis was reported (Scheme 1, route A).¹⁰ This approach utilised primary

amines, which when treated with chloroform in the presence of a strong base yielded isocyanides, albeit in poor yield of ~20%. A century later, the Hofmann procedure was modified by Weber and Gokel (Scheme 1, route B) to include the use of a phase transfer catalyst (PTC), benzyltriethylammonium chloride (BTEAC), in a biphasic system (50% aqueous sodium hydroxide/dichloromethane (DCM)), the latter of which hosts the primary amine and chloroform.⁴ This approach promotes the formation of benzyltriethylammonium hydroxide, which is soluble in both phases, and thereby promotes partitioning of the hydroxide ion into the organic phase initiating dichlorocarbene formation with the accompanying chloroform. The approach allowed the synthesis of various isocyanides in improved yields generally ranging from 40–60%.⁴ An alternative strategy was reported in 1956 by Hagedorn and Tonjes,¹¹ Hertler and Corey,¹² and Ugi and Meyr,¹³ involving the dehydration of mono-substituted formamides to afford isocyanides (Scheme 1, route C). By 1965, Ugi *et al.*¹⁴ refined the approach using a



Scheme 1 Commonly reported synthetic approaches to isocyanides.

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phosgene–triethylamine system. This general, two-step procedure involves the preparation of mono-substituted formamides by treatment of primary amines with formic acid or alkyl formates. This is followed by dehydration to afford isocyanides in yields ranging from 50–80%. The approach remains widely utilised today, and despite solubility issues, flow translations have been reported.^{15–19}

That being noted, the use of problematic and toxic dehydrating reagents phosgene^{14,18} and phosphorous oxychloride^{2,15–17,19} demerits the sustainability and safety of the method. Phosgene and phosphorus oxychloride are schedule 3 agents under the chemical weapons convention.²⁰ A status that's reserved for chemicals that are considered toxic warfare agents (phosgene) or precursors of warfare agents (phosphorus oxychloride), but have large-scale industrial uses.

In recent times, the adoption of flow chemistry has revitalised many forgotten and forbidden reactions.²¹ Bearing this in mind and considering that biphasic systems benefit from improved mass transfer afforded by flow systems, we hypothesised that we could develop a flow approach to revitalise the Hofmann carbylamine synthesis. This revitalisation was attractive as it uses cheaper, commercially available starting materials, is safer, and generates less toxic waste. Herein, we report a continuous flow solution for preparing isocyanides in good yields, which, to the best of our knowledge is the first reported Hofmann carbylamine synthesis on a microfluidic platform.

An initial validation of a model Hofmann carbylamine reaction was performed under batch conditions using a protocol reported by Cao *et al.* (Table 1).¹ The approach involved refluxing a 1:1 mol equivalence of 2-phenylethylamine **1** and chloroform (~3.2 M) in DCM with aqueous sodium hydroxide (50% w/w), in the presence of catalytic BTEAC, affording 2-isocianoethylbenzene **2** in a 41% isolated yield (Table 1, entry 1). The reaction was unfortunately accompanied by the

formation of a thick precipitate which was not amenable for flow translation; however, reducing the concentration of the aqueous sodium hydroxide to ≤ 12.5 M afforded a largely homogeneous solution, albeit at the expense of slightly lowered yields (entries 2–5). Comparatively, increasing the reaction time from 4 to 18 h afforded increased yields in the range of 55–60%, depending on the concentration of the aqueous sodium hydroxide employed (entries 6–8). Interestingly, as part of the downstream processing, the approach utilised an acid wash; however, the use thereof has previously been reported to cause unwanted hydrolysis of isocyanides.² Avoiding this acid work-up while concurrently doubling the concentration of the 2-phenylethylamine 1:chloroform mix led to a marked increase in yield to 72% when a 25 M NaOH_(aq) solution was utilised (entry 9). Despite the comparatively lower yields (and the slow reaction times) when performed at NaOH_(aq) concentrations of 12.5 M or lower, we still felt that a flow translation, at a comparable concentration, would greatly increase reaction efficiency due to the associated increase in interfacial contact area that would be afforded. Finally, for benchmarking purposes, 2-isocianoethylbenzene **2** was also prepared under batch conditions using the formamide/dehydration approach. In this instance, 2-phenylethylamine **1** was refluxed neat in the presence of ethyl formate (2.5 eq.) over 18 h to prepare the formamide. Thereafter, the formamide was taken up in DCM and treated with excess triethylamine (5.0 eq.) and phosphorus oxychloride (1.0 eq.) at 0 °C over 10–15 min affording **2** in 83% yield over two steps.

The flow protocol adopted aspects of the approach by Kappe and co-workers who previously prepared and reacted dichlorocarbene with alkenes to access *gem*-dihalocyclopropane's under flow conditions.²² In our approach, we utilised a Vapourtec R2S+/R4 reactor fitted with peristaltic pumps and the “blue” fluoro elastomer-based peristaltic tubing from Vapourtec (product code: 50-1301). The use of peristaltic pumps was required as the viscous nature of the reaction matrix prohibited the use of more commonly employed HPLC pumps. Initially, as we were concerned about the viscosity of the NaOH_(aq) solution and in-line precipitation, we elected to start optimisations at a lower concentration point for NaOH_(aq) (7.5 M). NaOH_(aq) was reacted with a 1.65 M solution of amine **1** in dichloromethane (containing 0.01 eq. BTEAC). The reagent lines were combined at a Y-piece mixer in a 1:1 ratio prior to passage through a 10 mL coil reactor (id = 1.0 mm, T_{res} = 50 min, temp = 80 °C) followed by an adjustable back pressure regulator. The product stream was collected directly in a separatory funnel, pre-loaded with distilled water for offline work-up and purification. The approach afforded isocyanide **2**, albeit in a low yield of 35%, despite a generous residence time of 50 min (Table 2, entry 1).

We next increased the reactor temperature to 110 °C affording an increase in yield to 44% (entry 2) and thereafter, doubling the residence time (adding an additional 10 mL coil reactor in series) under the same conditions resulted in a further increase in yield to 53% (entry 3). At this point,

Table 1 The model Hofmann carbylamine reaction performed under batch conditions

		i) CHCl ₃ (1 eq.)			
		BTEAC (1 mol%), DCM			
		ii) NaOH (aq), iii) Δ, 4-18 h			
				2	
No.	[NaOH] _(aq) ^a	[1] ^{a,b}	Time (h)	% yield	
1	50% w/w	3.17	4	41	
2	25.0	1.65	4	39	
3	15.0	1.65	4	37	
4	12.5	1.65	4	35	
5	10	1.65	4	36	
6	25.0	1.65	18	60	
7	15.0	1.65	18	56	
8	12.5	1.65	18	55	
9	25.0	3.30	4	72	

^a Organic and aqueous phases combined in a 1:1 v/v ratio (60 mL total volume entry 1; 10 mL total volume entries 2–9).

^b Concentration in DCM.



optimisation options were limited as the yields were poor to modest at best and i) the residence time was already too long for appreciable productivity, and ii) access to higher reaction temperatures (>110 °C) was not feasible as the system pressure was already approaching the maximum recommended operating pressure for the peristaltic pumps.

In response to introduce greater concentrations of the base without clogging the reactor, we opted to replace the 10 mL coil reactors with a wider bore 52 mL coil reactor (id = 2.1 mm). We elected to increase of the surficial contact area between the organic and aqueous phases by increasing the ratio of the NaOH_(aq) stock solution relative to the amine **1** stock from 1:1 to 2:1 which increased the size of the aqueous slugs relative to the organic slugs. Unfortunately, even when performed at a longer residence time of 150 min there was no improvement (entry 4). The Y-piece mixer was then exchanged for a 1.5 mL Vapourtec mixing chip while concurrently increasing the NaOH concentration to 8.75 M and the amine **1** concentration to 2.2 M. In this instance, the slugs produced appeared more uniform visually; however, the yield remained modest at 46% (entry 5). Surprisingly, precipitation remained limited and did not prove to be an issue when compared with the smaller internal diameter 10 mL coil reactors, so we next increased the NaOH_(aq) concentration further to 12.5 M. As we remained concerned about in-line precipitation, we also included a water quench line and dissolution loop between the coil reactor and the BPR to ensure the solution was homogeneous prior to passage through the BPR. The precipitation build-up remained limited, and the yield increased to 57% at a reduced residence time of 60 min (entry 6).

The concentration of the NaOH_(aq) solution was increased again to 15 M and the amine **1** stock solution was increased to 2 M (containing 0.02 eq. BTEAC), and at a 1:1 ratio the yield was increased to 62% ($T_{\text{res}} = 60$ min, temp = 110 °C) (entry 7). Increasing the flow rate, coupled with an increased aqueous:organic flow ratio, had the added advantage of

reducing the size of the reaction slugs resulting in steadily increasing yields culminating at 70% with a residence time of only 15 min when performed at 110 °C (entries 8 and 9). Unfortunately, the increasing flow rate resulted in a steady increase in the system pressure which prevented further reductions in the residence time.

At this stage, the basic scalability of the approach was assessed. In this instance, the model amine **1** was used as a demonstrator and the reaction was performed in triplicate at a 10 g scale (entry 11). Notably in this instance, the concentration of NaOH_(aq) was reduced to 15 M, and the 52 mL coil reactor was heated to 110 °C. The approach allowed the preparation of isocyanide **2** in an average isolated yield of 75%. Notably, increasing the temperature to 110 °C in this instance, although successful required operating at close to the pressure limits of the peristaltic pumps. As a result, we reverted to the previous conditions for further studies.

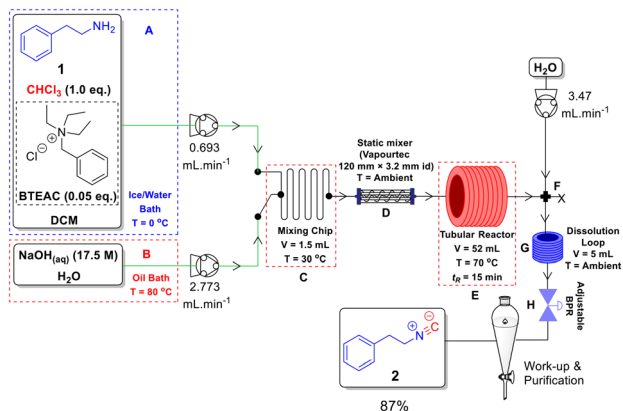
The final reactor set-up (entry 11, Scheme 2 and Fig. 1) utilised two reagent reservoirs connected upstream relative to two peristaltic pumps fitted with the “blue” fluoroelastomer-based peristaltic tubing. The first reservoir A contained a 1:1 mol equivalent mix of amine **1** and chloroform in DCM (2.0 M) and 0.05 eq. of BTEAC. As volatile chloroform was used stoichiometrically, the reservoir was cooled to 0 °C as a precaution to limit its loss to the reservoir headspace. The second reservoir B contained a solution of aqueous sodium hydroxide (17.5 M) and was heated to 80 °C to ensure homogeneity and reduce the viscosity of the solution prior to entry into the reactor. The flow paths were combined downstream in a 1.5 mL Vapourtec mixing chip C (temp = 30 °C, $T_{\text{res}} = 43$ s) connected in series with a Vapourtec static mixer D (120 mm × 3.2 mm id); the use of these mixing elements served to reduce the size of the organic/ aqueous slugs and maximise the interfacial contact area. To minimise temperature loss/gain, all flow path tubing (highlighted in green in Scheme 2) from the reservoirs to the mixing chip were wrapped in insulating silicone tape (Alcolin Silicone Tape; 25 mm × 3 m). The flow stream was

Table 2 The model Hofmann carbylamine reaction performed under flow conditions

No.	[NaOH] _(aq)	[1]	BTEAC eq.	Mixer type	Flow rate ratio A:B:(C) ^a	T_{res} (min)	Temp (°C)	% yield ^b
1	7.5	1.65	0.01	Y-piece	1:1	50 ^d	80	35
2	7.5	1.65	0.01	Y-piece	1:1	50 ^d	110	44
3	7.5	1.65	0.01	Y-piece	1:1	100 ^d	110	53
4	7.5	1.65	0.01	Y-piece	1:2	150 ^e	110	49
5	8.75	2.2	0.01	Chip ^c	1:2	150 ^e	110	46
6 ^f	12.5	1.56	0.01	Chip ^c	1:1:2	60 ^e	110	57
7 ^f	15.0	2.0	0.02	Chip ^c	1:1:4	60 ^e	110	62
8 ^f	15.0	2.0	0.02	Chip ^c	1:3:4	30 ^e	110	65
9 ^f	15.0	2.0	0.02	Chip ^c	1:3:4	15 ^e	110	70
10 ^{f,g}	15.0	2.0	0.05	Chip ^c	1:3:4	15 ^e	110	75 ^h
11 ^{f,i}	17.5	2.0	0.05	Chip ^c	1:4:5	15 ^e	70	87 ^j

^a A = stock containing **1** and BTEAC in DCM, B = aqueous NaOH stock, C = H₂O quench. ^b Isolated yields unless noted. ^c 1.5 mL Vapourtec mixing chip. ^d 10 mL coil reactor (id = 1.00 mm). ^e 52 mL coil reactor (id = 2.1 mm). ^f Water quench line inserted between the coil reactor and BPR. ^g 10 g scale. ^h Performed in triplicate, average yield. ⁱ NaOH_(aq) stock solution pre-heated to 80 °C prior to introduction to the reactor. ^j Conversion determined by qNMR.





Scheme 2 General flow scheme for the preparation of isocyanides.

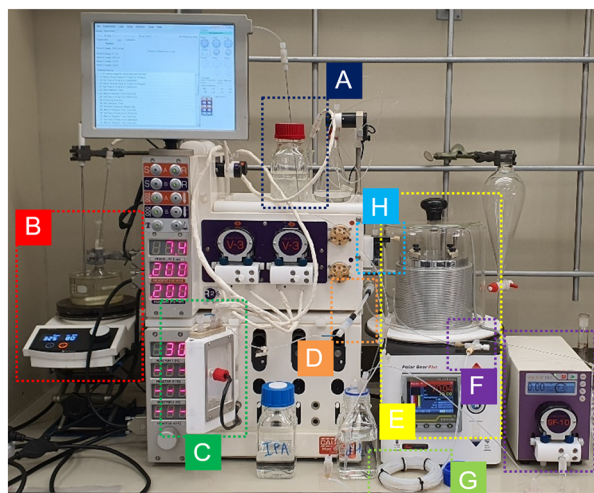


Fig. 1 Photograph of the reactor set-up with colour coded outlines for ease of reference to Scheme 2.

then directed through a PTFE coil reactor E ($V = 52$ mL, $id = 2.1$ mm, $Temp = 70$ °C, $T_{res} = 15$ min), after which it was combined at an X-piece mixer (stoppered at one end) F with a water quench line followed by a 5 mL dissolution loop G. The latter was required to ensure that any trace solids were dissolved prior to passage through the adjustable back pressure regulator H. The product stream was collected directly in a separatory funnel, and following the phase separation, the DCM layer was removed. Additional extractions of the aqueous phase and back washing of the combined organics were performed offline. The combined organic layers were then dried and filtered, and finally the filtrate was passed through a silica plug (dry vacuum column chromatography) followed by additional portions of DCM. The setup as described afforded the preparation of the model (2-isocianoethyl)benzene **2** in 87% conversion (based on qNMR- H^1 analysis). Notably, we were able to i) increase the concentration of the aqueous sodium hydroxide solution to 17.5 M without any deleterious precipitation events, and ii) reduce the residence time to only 15 min. At lower flow rates (longer residence times), mixing efficiency

reduced causing larger slugs with reduced surficial contact. A 1:4 flow ratio of A:B proved the most effective to generate sufficiently small slugs of DCM to afford good conversions. In summary, highly concentrated stocks were preferred as they ensured rapid dichlorocarbene formation. It is important to note that the reactions were not analysed under steady-state conditions, instead the entire plug was collected and analysed. Notwithstanding, we opted to approximate steady state pumping by introducing the aqueous sodium hydroxide stream ahead of the main plug and thereafter ended it after the main plug (see the SI for experimental details).

Following this result, we used the setup and optimised conditions to prepare a diverse series of isocyanides **3–23**, to assess the scope and robustness (Fig. 2). We first reduced the length of the alkyl chain in **1** to access the benzylic **3** and aryl **4** isocyanides in good conversions of 80% and 85%, respectively. We then decided to attempt the reaction using *ortho*-, *meta*-, and *para*-chloro anilines. In all three cases, appreciable conversions were achieved, with the *para*- (>99%) and *ortho*- (94%) analogues **5** and **6** outperforming the *meta*- (80%) analogue **7**. The difference in reactivity arises as the *ortho*- and *para*-derivatives **5** and **6** can activate the aniline amine through resonance electron donation. Alternatively, when using *para*-methyl aniline, which is only capable of inductively activating the aromatic ring, a conversion of 85% for **8** was achieved, which was comparable to that achieved when preparing **4** from aniline. Unsurprisingly, when changing to a strong resonance deactivator (*para*-nitroaniline), the conversion decreased to 29% for the preparation of **9**. In contrast, strongly activated 1,3-benzodioxole derivative **10** afforded a high conversion of 87%.

We then turned our attention to the preparation of aliphatic amines starting with *n*-propylamine, *n*-butylamine and *n*-dodecylamine as representative examples affording the desired isocyanides **11–13** in 54, 74 and 93% conversions, respectively. The observed trend is supported by the fact that the preferential ion-dipole intermolecular forces between sodium hydroxide and water are favoured over the dipole-dipole hydrogen interactions between the amine and water. Consequently, this promotes the partitioning of the amine into the organic phase; however, as the hydroxide ions are consumed during the reaction, some of the amine partitions into the aqueous phase, and thereafter is lost during post-reaction phase separation. The trend is exacerbated as the water solubility of the amine increases, as such we observed the conversions decreasing as the aliphatic chain length decreases and the amine becomes more polar in nature. An additional cyclic aliphatic isocyanide **14** was also prepared in a good conversion of 81%.

We then prepared 1-(2-isocianoethyl)cyclohex-1-ene **15**, 3-isociano-3-methylbut-1-yne **16** and ethyl(2-isocianoethyl)sulfane **17** as examples containing an alkene, alkyne and thioether functionality. In all three cases, good conversions were observed. Notably, in the case of **15**, the isocyanide was



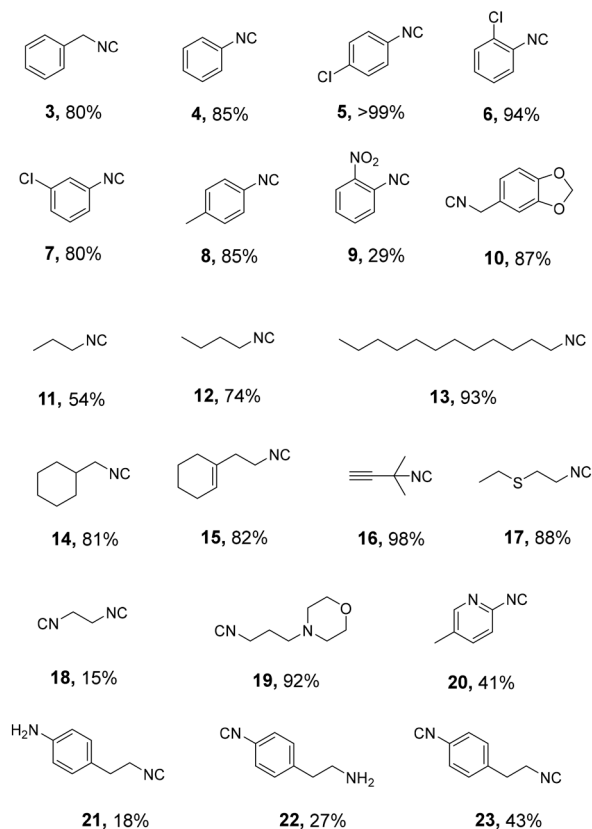


Fig. 2 Range of isocyanides prepared using the optimised flow conditions. qNMR conversions reported.

prepared regioselectively with no cycloaddition to the *gem*-dihalocyclopropane as reported previously by Kappe and co-workers; this selectivity is likely arising as the approach developed only utilises chloroform stoichiometrically, *vs.* Kappe and co-workers who used it as a carrier solvent.²² Thereafter, an attempt to prepare 1,2-diisocynoethane **18** proved challenging due to the high aqueous solubility of the diamine resulting in a low conversion of only 15%.

It was then decided to prepare polar isocyanide examples **19** and **20**, with tertiary amine containing morpholine derivative **19** affording an appreciable conversion of 92%. Although this tertiary amine example responded well, the heteroaryl picoline derivative **20** only afforded a modest conversion of 41%. That being noted, the modest yield is not unexpected as the picoline starting material has an electron deficient amine.

Finally, we decided to assess if the approach would afford a degree of regioselectivity when starting with a diamine containing an arylamine (aniline) moiety and alkylamine (ethylamine) moiety. The approach facilitated good overall conversion; however, there was no appreciable selectivity with **21**, **22** and **23** prepared in a 1 : 1.5 : 1.06 mol eq. ratio.

Finally, to ascertain if the newly developed approach would afford an economic advantage over the alternative two step formamide/dehydration approach, a cost and mass analysis (see SI) was performed. The model isocyanide **2** was

selected as an example for analysis and the cost of raw materials employed to produce **2** was calculated for i) the Hofmann approach under batch conditions (Table 3, entry 1), ii) the Hofmann approach under flow conditions (entry 2) and iii) the two step formamide/dehydration approach under batch conditions (entry 3). As the downstream processing and purification for entries 1 and 3 were not fully optimised in-house, and wishing to avoid bias, we elected to only consider the cost of raw materials (reagents and solvents) employed and did not include the cost of materials employed in downstream processing operations. The outcome of the analysis suggested that the developed flow approach would allow the preparation of isocyanides at ~9% lower cost point based on the three scenarios considered.

In summary, we have developed a convenient flow approach for preparing isocyanides easily and in good conversion by revitalising the largely forgotten Hofmann carbylamine reaction. The flow approach shows improvement over the analogous batch alternative through improved yield, reduced residence time (*vs.* reaction time) and reduced cost. The latter arising due to the increased yield and reduced stoichiometries of NaOH and DCM employed. Additionally, the developed approach affords several advantages over the more commonly utilised formamide/dehydration approach including:

i) The process uses low cost, commercially available reagents allowing the preparation of isocyanides at a lower cost point.

ii) The process has a short reaction residence time of 15 min *vs.* >18 h reaction time for the formamide/dehydration approach. This is reflected in the associated space time yields of 83.5 and 3.67 g L⁻¹ h⁻¹, respectively for the two approaches.

iii) The process appears to be more favourable from an energy use point-of-view avoiding the extensive refluxing required in the formamide/dehydration approach.

iv) It is more attractive from a waste perspective having reduced toxicity within the process structure, and it does not generate phosphorus salts as by-products which can prove challenging to downstream processing.

v) In terms of health and safety, the process notably avoids the use of problematic phosphorus oxychloride (or phosgene) and diethyl ether. The developed flow approach does rely on the use of undesirable chloroform and DCM. In the case of chloroform, the reagent is only used stoichiometrically and is mechanistically required serving as the source of the carbon in the isocyanide group. In the case of DCM, our investigations suggested that its use is necessary to ensure

Table 3 Cost analysis of Hofmann and formamide/dehydration approaches for preparing isocyanides

No.	Approach ¹	Mode	Cost per kg (USD)
1	Hofmann	Batch	106.5
2	Hofmann	Flow	96.7
3	Formamide/dehydration	Batch	109.3



adequate conversion and allow an operationally simple work-up and purification.

vi) The process has fewer steps (1 vs. 2), is easily automated, and has a comparably simpler work-up and purification.

vii) The formation/use of dichlorocarbene can present limitations in terms of exothermicity; however, in the case in hand we did not observe any significant temperature fluctuations.

In addition, from a flow perspective, the approach is not plagued by precipitation issues, and we believe the method will serve as a useful and cheaper alternative for the preparations of isocyanides.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the supplementary information (SI).

Supplementary information: including experimental details, characterising data and techno-economic data. See DOI: <https://doi.org/10.1039/d5re00338e>.

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References

- H. Cao, H. Liu and A. Dömling, Efficient multicomponent reaction synthesis of the Schistosomiasis drug praziquantel, *Chem. – Eur. J.*, 2010, **16**(41), 12296–12298, DOI: [10.1002/chem.201002046](https://doi.org/10.1002/chem.201002046), WorldCat.org.
- P. Patil, M. Ahmadian-Moghaddam and A. Dömling, Isocyanide 2.0, *Green Chem.*, 2020, **22**(20), 6902–6911.
- U. Galli, G. C. Tron, B. Purghè, G. Grosa and S. Aprile, Metabolic fate of the isocyanide moiety: Are isocyanides pharmacophore groups neglected by medicinal chemists?, *Chem. Res. Toxicol.*, 2020, **33**(4), 955–966, DOI: [10.1021/acs.chemrestox.9b00504](https://doi.org/10.1021/acs.chemrestox.9b00504), WorldCat.org.
- W. P. Weber and G. W. Gokel, An improved procedure for the Hofmann carbylamine synthesis of isonitriles, *Tetrahedron Lett.*, 1972, **13**(17), 1637–1640, DOI: [10.1016/S0040-4039\(01\)84707-9](https://doi.org/10.1016/S0040-4039(01)84707-9), WorldCat.org.
- F. Y. Lim, T. H. Won, N. Raffa, J. A. Baccile, J. Wisecaver, A. Rokas, F. C. Schroeder and N. P. Keller, Fungal isocyanide syntheses and xanthocillin biosynthesis in *aspergillus fumigatus*, *mBio*, 2018, **9**(3), e00785-18, DOI: [10.1128/mBio.00785-18](https://doi.org/10.1128/mBio.00785-18), WorldCat.org.
- C. E. Arcadia, E. Kennedy, J. Geiser, A. Dombroski, K. Oakley, S.-L. Chen, L. Sprague, M. Ozmen, J. Sello and P. M. Weber, *et al.*, Multicomponent molecular memory, *Nat. Commun.*, 2020, **11**(1), 691, DOI: [10.1038/s41467-020-14455-1](https://doi.org/10.1038/s41467-020-14455-1), WorldCat.org.
- S. Javanbakht and A. Shaabani, Multicomponent reactions-based modified/functionalized materials in the biomedical platforms, *ACS Appl. Bio Mater.*, 2020, **3**(1), 156–174, DOI: [10.1021/acsabm.9b00799](https://doi.org/10.1021/acsabm.9b00799), WorldCat.org.
- E. Fotopoulou, P. K. Anastasiou, C. Tomza and C. G. Neochoritis, The Ugi reaction as the green alternative towards active pharmaceutical ingredients, *Tetrahedron Green Chem*, 2024, **3**, 100044, DOI: [10.1016/j.tgchem.2024.100044](https://doi.org/10.1016/j.tgchem.2024.100044), ScienceDirect.
- W. Lieke, Ueber das cyanallyl, *Justus Liebigs Ann. Chem.*, 1859, **112**(3), 316–321, DOI: [10.1002/jlac.18591120307](https://doi.org/10.1002/jlac.18591120307), WorldCat.org.
- A. W. Hofmann, Ueber eine neue reihe von homologen der cyanwasserstoffsäure, *Justus Liebigs Ann. Chem.*, 1867, **144**(1), 114–120, DOI: [10.1002/jlac.18671440116](https://doi.org/10.1002/jlac.18671440116), WorldCat.org.
- I. Hagedorn and H. Tonjes, Konstitutions-aufklärung von xanthocillin, einem neuen antibioticum, *Pharmazie*, 1956, **11**(6), 409–410, WorldCat.org.
- W. Hertler and E. Corey, A novel preparation of isonitriles, *J. Org. Chem.*, 1958, **23**(8), 1221–1222, DOI: [10.1021/jo01102a612](https://doi.org/10.1021/jo01102a612), WorldCat.org.
- I. Ugi and R. Meyr, Neue darstellungsmethode für isonitrile, *Angew. Chem., Int. Ed. Engl.*, 1958, **70**(22–23), 702–703, DOI: [10.1002/ange.19580702213](https://doi.org/10.1002/ange.19580702213), WorldCat.org.
- I. Ugi, U. Fetzer, U. Eholzer, H. Knupfer and K. Offermann, Isonitrile syntheses, *Angew. Chem., Int. Ed. Engl.*, 1965, **4**(6), 472–484, DOI: [10.1002/anie.196504721](https://doi.org/10.1002/anie.196504721), WorldCat.org.
- C. E. Salvador, B. Pieber, P. M. Neu, A. Torvisco, Z. A. C. Kleber and C. O. Kappe, A sequential Ugi multicomponent/Cu-catalyzed azide-alkyne cycloaddition approach for the continuous flow generation of cyclic peptoids, *J. Org. Chem.*, 2015, **80**(9), 4590–4602, DOI: [10.1021/acs.joc.5b00445](https://doi.org/10.1021/acs.joc.5b00445), WorldCat.org.
- S. Sharma, R. A. Maurya, K.-I. Min, G.-Y. Jeong and D.-P. Kim, Odorless isocyanide chemistry: An integrated microfluidic system for a multistep reaction sequence, *Angew. Chem.*, 2013, **125**(29), 7712–7716, DOI: [10.1002/ange.201303213](https://doi.org/10.1002/ange.201303213), WorldCat.org.
- S. Chen, M. Oliva, L. Van Meervelt, E. V. Van der Eycken and U. K. Sharma, Palladium-catalyzed domino synthesis of 2, 3-difunctionalized indoles via migratory insertion of isocyanides in batch and continuous flow, *Adv. Synth. Catal.*, 2021, **363**(13), 3220–3226, WorldCat.org.
- M. Baumann, A. M. Rodriguez Garcia and I. R. Baxendale, Flow synthesis of ethyl isocyanoacetate enabling the telescoped synthesis of 1,2,4-triazoles and pyrrolo-[1,2-c]



- pyrimidines, *Org. Biomol. Chem.*, 2015, **13**(14), 4231–4239, DOI: [10.1039/c5ob00245a](https://doi.org/10.1039/c5ob00245a).
- 19 B. Cerra, C. Blondeau, R. Cannalire, M. Giustiniano, S. Tali Shandiz and A. Gioiello, Isocyanide chemistry enabled by continuous flow technology, *React. Chem. Eng.*, 2023, **8**(3), 656–660, DOI: [10.1039/D2RE00454B](https://doi.org/10.1039/D2RE00454B).
- 20 OPCW, (Organisation for the Prohibition of Chemical Weapons) Annex on Chemicals, Schedule 3, 2024, <https://www.opcw.org/chemical-weapons-convention/annexes/annex-chemicals/schedule-3> (accessed 19/10/2024).
- 21 A. Bonner, A. Loftus, A. C. Padgham and M. Baumann, Forgotten and forbidden chemical reactions revitalised through continuous flow technology, *Org. Biomol. Chem.*, 2021, **19**(36), 7737–7753, DOI: [10.1039/d1ob01452h](https://doi.org/10.1039/d1ob01452h).
- 22 T. von Keutz, D. Cantillo and C. O. Kappe, Enhanced mixing of biphasic liquid-liquid systems for the synthesis of gem-dihalocyclopropanes using packed bed reactors, *J. Flow Chem.*, 2019, **9**(1), 27–34, DOI: [10.1007/s41981-018-0026-1](https://doi.org/10.1007/s41981-018-0026-1), Springer Nature.

