



Cite this: *React. Chem. Eng.*, 2023, 8, 656

Received 27th October 2022,
Accepted 28th November 2022

DOI: 10.1039/d2re00454b

rsc.li/reaction-engineering

Isocyanide chemistry enabled by continuous flow technology†

Bruno Cerra,^a Cecile Blondeau,^a Rolando Cannalire,^b Mariateresa Giustiniano,^b Shiva Tali Shandiz^a and Antimo Gioiello^{id}*^a

Isocyanides are valuable compounds for organic synthesis. However, the poor stability and distressing odour have often limited their widespread applications in common laboratory practice and industrial settings. Herein, a continuous flow approach to enable the synthesis, purification and in-line reaction of isocyanides is presented.

Isocyanides are important and versatile compounds with a long history in organic synthesis and production of chemicals.¹ Currently, the global isocyanide market surges to more than 5% per year, underlining its relevance in agrochemicals and pharmaceuticals. Their divalent nature and ability to form multiple bonds on the terminal carbon make them a multifaceted group for organic synthesis with broad applications in medicinal chemistry.² Indeed, the potential of isocyanide-based chemistry and related post-modification reactions has been demonstrated in both target- and diversity-oriented synthesis. However, several issues have barred their wide use in both academia and industry. Some isocyanides, such as the volatile ones, are characterized by a) strong foul odour, b) sensitivity to moisture, c) poor stability and d) potential toxicity.

Isocyanides are produced industrially using phosgenation of alkyl or aromatic amines.³ However, the high toxicity of the gas raises safety concerns and requires special equipment. Other methods such as the Curtius rearrangement, and the Lieke–Meyer, Hoffmann, and Ugi reactions are generally employed in common laboratory practise.^{1,2} Although many other options exist, the vast majority of isocyanide syntheses still suffer from one or more issues including tedious protocols and work-up operations, expensive reagents, waste generation, and exposure to potentially hazardous fumes.

In the last few years, continuous flow chemistry has greatly facilitated the development of safe and efficient approaches for conducting forbidden chemical reactions.⁴

Adoption of flow synthesizers has been a determinant in moving towards green chemistry and more sustainable practices.⁵ In addition to improved process safety and quality, flow chemistry guarantees the fine-tuning of the reaction conditions, an efficient heat and mass transfer, and an extended operative window.⁶ Furthermore, the possibility to perform telescoped reactions and to integrate downstream operations avoids intermediate isolation, minimizing the exposure to toxic and hazardous reagents with a great improvement to the safety and environmental impacts.⁴ The merger of these benefits with automation promises to accelerate the development of new synthetic routes and compound throughput relieving expert chemists of routine tasks.⁷

In a previous work, Kim and colleagues reported the preparation of isocyanides in a microfluidic system with short reaction times and high yield.^{8a} However, the method suffered from solubility and tube-plugging issues that were partially solved using ultrasound irradiation. In 2015, Baxendale and co-workers reported the telescoped flow synthesis of different heterocyclic building blocks, including 1,2,4-triazole and pyrrolo[1,2-*c*]pyrimidine scaffolds, using ethyl isocyanacetate that was generated *in situ* by the dehydration reaction of *N*-formylglycine in the presence of triphosgene.^{8b}

In this work, we present a streamlined method based on reactor technology for the serial synthesis, purification, scale-up and in-line reaction of isocyanides. Such an approach would solve major drawbacks, enable the progress and expand the scope of isocyanide chemistry.⁹ Combination with various reagents is conducted in a continuous fashion to provide diverse building blocks and important products without requiring the isolation of highly unstable and foul odour volatile isocyanides.

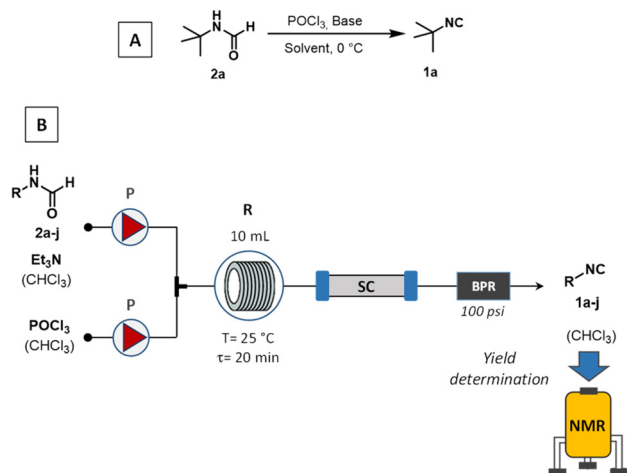
In order to set a benchmark with which our flow approach would be compared, we opted to conduct the Ugi synthesis of *t*-butyl isocyanide (**1a**) from the corresponding formamide **2a**,

^a Laboratory of Medicinal and Advanced Synthetic Chemistry (Lab MASC), Department of Pharmaceutical Sciences, University of Perugia, Via del Liceo 1, Perugia, 06123, Italy. E-mail: antimo.gioiello@unipg.it

^b Department of Pharmacy, University of Naples Federico II, Via D. Montesano 49, 80131, Napoli, Italy

† Electronic supplementary information (ESI) available: Details on experimental procedures, compound characterization and equipment are provided. See DOI: <https://doi.org/10.1039/d2re00454b>





Scheme 1 A) Batch synthesis of *t*-butyl isocyanide (**1a**) from the corresponding formamide **2a**. B) Flow synthesis and in-line purification of isocyanides. General flow set-up used for the preliminary reaction screening and to investigate the substrate scope. BPR: back pressure regulator; P: pump; R: 10 mL reactor coil; SC: packed silica gel column.

in the presence of phosphorus oxychloride (POCl_3) (1 equiv.) (Scheme 1A). Initially, diverse solvents (CHCl_3 , CH_2Cl_2 , THF, 2-Me-THF) and organic bases (Et_3N , DIPEA, pyridine, DIPA, TBA, DBU, DBN, proton sponge) were tested in batch modality to evaluate possible solubility issues and reactor clogging (data not shown). Most of the solvents and bases resulted in suspensions or in-line precipitation. Nevertheless, the desired *t*-butyl isocyanide (**1a**) was obtained in moderate to high yields. The best outcome was achieved with the use of CHCl_3 and Et_3N (5 equiv.) at 0°C which ensured a clear solution (up to 0.6 M) and a high yield (82%). The aqueous work-up required careful hydrolysis to destroy the possible excess of POCl_3 , keeping basic pH conditions to avoid isocyanide decomposition. The crude isocyanide should be then purified, increasing the exposure to smelly odour over a rather long period.

Next, the reaction was repeated under flow conditions. As depicted in Scheme 1B, the flow set-up consisted of two syringe pumps to combine a solution of **2a** (0.6 M solution in CHCl_3) and Et_3N with a stream of POCl_3 (0.6 M solution in CHCl_3) via a PEEK T-piece. A 20 mL PFA coil was used as the reactor, which was followed by a silica packed column for the in-line removal of salts and excess Et_3N .⁹ In order to avoid aqueous work-up in favour of a simple alternative, the collected reaction mixture was analysed by quantitative $^1\text{H-NMR}$, using dimethyl sulfone as an internal standard. The procedure allowed a simpler set-up in addition to enabling rapid flow processing of materials and post-modification reactions. It was found that running the reaction for 20 min at 25°C rendered the expected product **1a** in excellent yield (89%) (Table 1, entry 1). A partial conversion (65%) was obtained by reducing the Et_3N equiv. from 5 to 3. Using the best conditions, the reaction was proven effective in the multi-gram preparation of *t*-butyl isocyanide (**1a**) with a throughput of 3 mmol h^{-1} (Scheme 1B).

Table 1 Substrate scope and results for the flow synthesis and in-line purification of isocyanides

Entry	Isocyanide	Yield ^a	Literature yield
1	1a	89%	82% ^d
2	1b	87%	95% ⁹ 62% ¹⁰
3	1c	79%	67% ¹⁰
4	1d	69%	(-)
5	1e	Traces	(-)
6	1f	87% ¹¹	91% ¹²
7	1g	44% ^{b,c}	93% ⁹
8	1h	77%	97% ¹³
9	1i	79% ^b	81% ⁹
10	1j	80% ^c	97% ¹⁴

Reactions were performed according to Scheme 1. (-) = No literature available from formamide to isocyanide *via* dehydration under standard conditions. ^a Yield determined by calibrated $^1\text{H-NMR}$ analysis of the crude product in the presence of dimethyl sulfone as the internal standard. ^b DMSO (5%, v/v in CHCl_3) was used as the co-solvent, $[\mathbf{2g}] = 0.15\text{ M}$, $[\mathbf{2i}] = 0.36\text{ M}$. ^c Isolated yield. ^d Conducted by reaction of **1a** with POCl_3 (1 equiv.) and of Et_3N (5 equiv.) in CHCl_3 at 0°C until starting material consumption.

The method was applied to other *N*-substituted formamides **2b-j**, and the formation of isocyanides was nearly completed within 20 min (Table 1). The criteria for substrate selection include the extensive usage, high volatility, foul odour, and toxicity of the resulting isocyanides.⁹ As a general trend, the reaction allowed the formation of the desired isocyanides with high purity and in good to high yields, except for formamides **2e** and **2g** (Table 1, entries 5 and 7). While allyl isocyanide **1e** was formed in traces, the preparation of 2,6-dimethylphenyl isocyanide (**1g**) required the addition of 5% DMSO to ensure the complete solubility of the reaction mixture. Unfortunately, the use of DMSO caused the formation of solvent-derived by-products leading to a moderate reaction yield (44%) (Table S1, ESI†). In the case of aryl isocyanides,



both electron-donating and -withdrawing groups work similarly well (entries 8 and 9). Comparison of our results with the ones reported in the literature under standard conditions has evidenced similar yields with a few exceptions; however, it should be pointed out that for these cases, the preparation required a long reaction time (24 h) and tedious protocols.

Having established a reliable flow method for the preparation and purification of pure isocyanides, our efforts were then focussed on the development of a flow system enabling in-line capture. The flow set-up has been designed to allow the serial synthesis of relevant scaffolds in medicinal chemistry (Scheme 2). The synthesizer was composed of a pump system, switching/mixing devices, two 10 mL coil reactors, back pressure regulators (BPRs), an autosampler, a UV detector, an automated flash chromatograph, and a fraction collector. Three sets of compounds, including 5-aminoimidazoles, 1,3-oxazoles, and β -amino amides such as the anaesthetic lidocaine, were prepared to showcase the feasibility of the flow system, using standard, non-optimized process conditions. At this stage, we aim to demonstrate the merging and compatibility of the reaction conditions and solvents between steps. This reaction scoping also served to assess the robustness of the processing conditions against the propensity for blockage formation.⁸ Notably, at the concentration studied for the flow set-up, no blockages

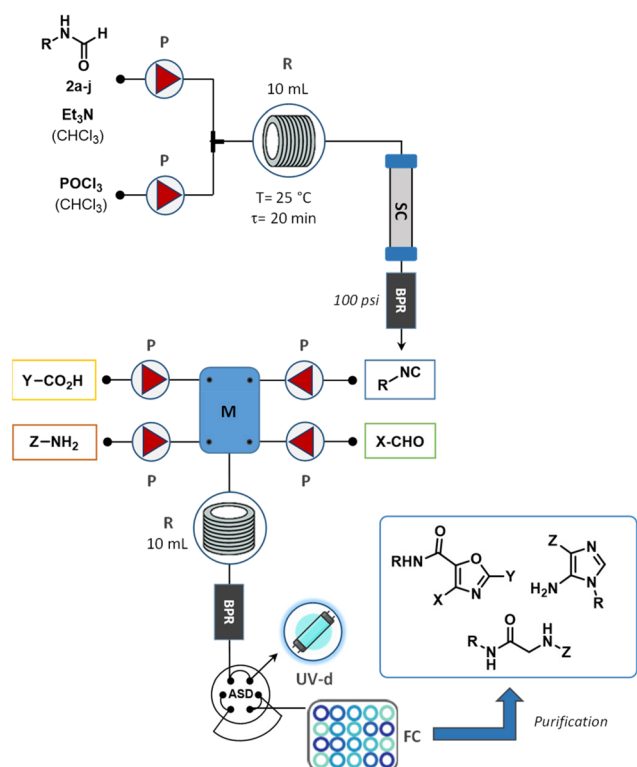
occurred across the screened substrates and reactions. By not performing all steps simultaneously, the flow rates, concentrations, and temperatures can be easily adjusted without changing the equipment. Moreover, to permit reaction monitoring, and product detection and collection, an aliquot of the exit stream was analysed using a UV detector.

1,3-Oxazoles

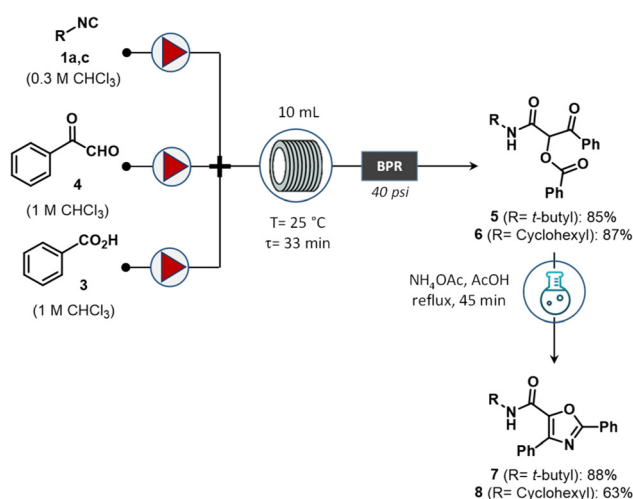
1,3-Oxazoles are an important class of pharmaceutically interesting heterocycles, and consequently, many synthetic protocols have been reported to access their structures.¹⁵ In-flow examples include a three-step method from vinyl azides¹⁶ and a fully automated flow synthesis by the reaction of alkyl isocyanides with acyl chloride followed by intramolecular cyclization.¹⁷ In our case, we sought to explore the Passerini-cyclization reaction sequence to obtain trisubstituted 1,3-oxazoles (Scheme 3). Thus, isocyanide **1a** or **1c**, prepared as previously described, was collected into an Erlenmeyer flask with a screw cap, pumped at 0.18 mL min^{-1} and mixed in a four-way connector with a solution of benzoic acid (**3**) and phenylglyoxal (**4**). The reaction mixture was reacted into a 10 mL coil reactor at $25 \text{ }^\circ\text{C}$ ($\tau = 33 \text{ min}$) affording the corresponding intermediates **5** and **6** in high yield (85% and 87% yield, respectively) after out-flow crystallization (Scheme 3). Cyclisation of the Passerini adducts **5** and **6** was performed using NH_4OAc in AcOH (5 M) under reflux for 45 min. Simple filtration of the solid products afforded the desired oxazole derivatives **7** and **8** in 75% and 52% yield, respectively, over two steps (Scheme 3). Notably, batch synthesis using the same reaction conditions provided **8** in 28% overall yield.¹⁸

5-Aminoimidazoles

Despite their potential in the synthesis of bioactive compounds, only a few methods have been reported for the

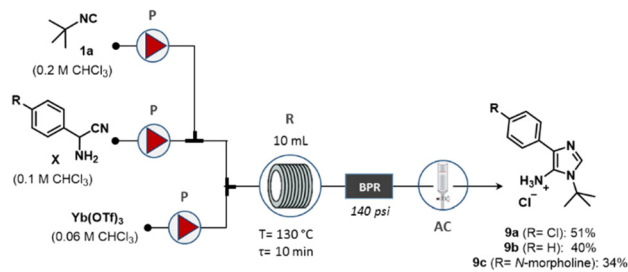


Scheme 2 Integrated flow system for enabling isocyanide chemistry. ASD: autosampler; BPR: back pressure regulator; FC: fraction collector; M: mixer/switching device; P: pump; R: reactor coil; SC: silica gel packed column; UV-d: UV detector.

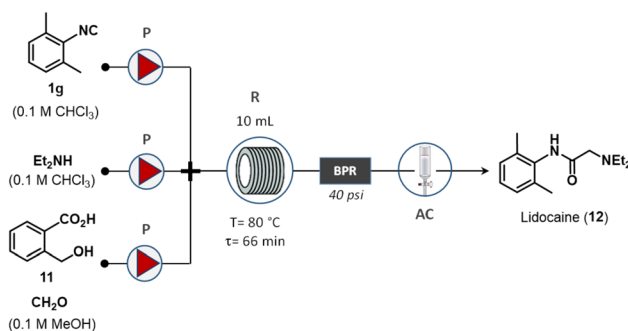


Scheme 3 Flow synthesis of 1,3-oxazoles from isocyanides **1a** and **1c**.





Scheme 4 Flow synthesis of 4-substituted-5-aminoimidazoles from *t*-butyl isocyanide (**1a**).



Scheme 5 Flow synthesis of lidocaine (**12**) by the Ugi reaction.

preparation of 5-aminoimidazoles.^{19,20} We recently described the ytterbium-promoted isocyanide insertion/*exo-dig* cyclization of Strecker adducts towards 4-substituted 5-aminoimidazoles.²¹ In the course of the investigation, we noticed a certain compound instability that may limit their exploitation to further chemical manipulations. This could be overcome with the recourse to continuous flow technology. Thus, a CHCl_3 solution of isocyanide **1a** from step 1 (Scheme 1B, Table 1) was first mixed with a CHCl_3 solution of α -aryl- α' -amino-acetonitriles **9a–c** (1 equiv.) with a total flow rate of 0.5 mL min^{-1} . The resulting solution was then mixed through a T-junction with $\text{Yb}(\text{OTf})_3$ dissolved in CHCl_3 . The reaction took place in a 10 mL coil reactor heated at $130 \text{ }^\circ\text{C}$ ($\tau = 10 \text{ min}$) (Scheme 4). The reactor outcome was collected, readily purified by automated chromatography, and converted into the corresponding hydrochloride salt for improving product stability. The reactions gave the expected 4-aryl-5-aminoimidazoles **9a–c** in 34–51% yields.

Lidocaine

Lidocaine (**12**), also known as xylocaine, is a commonly used local anesthetic and antiarrhythmic drug. Seeking to avoid the elevated reaction temperatures and chloroacetyl chloride employed in the traditional *N*-acylation/*N*-alkylation approach, we sought to adapt the Ugi multicomponent synthesis of lidocaine (**12**) to our flow method. Thus, the CHCl_3 solution of **1g** (0.1 M) collected from the previous step into a sealed Erlenmeyer flask was mixed with a solution of

Et_2NH (1 equiv.) and 2-hydroxymethylbenzoic acid (**11**) (1 equiv.) premixed with formaldehyde (1 equiv.) (Scheme 5). The mixture was reacted into a 10 mL coil reactor ($\tau = 66 \text{ min}$) at $80 \text{ }^\circ\text{C}$. The outflow was collected and readily purified by automated flash chromatography to give pure lidocaine (**12**) in 69% yield (0.1 mmol h^{-1}) (Scheme 5). Compared to conventional multi-step approaches for preparing lidocaine,²² this multicomponent telescoped protocol offers superior atom- and step-economy, eliminates the need for hazardous heating sources and solvent intensive extraction steps, employs readily starting materials and is easy to perform. Moreover, our approach is amenable for automation and can be employed for the rapid, diverse, and parallel synthesis of commercial and novel local anesthetics based on the amide-caine scaffold.

Conclusions

New methods are needed for maximizing resource-accelerated synthesis and medicinal chemistry, which are areas where continuous flow chemistry can demonstrate distinct benefits.²³ Enabling repetitive and trivial reaction sequences accelerates processing method development, especially when integrated with diverse units and downstream operations, telescoping approaches and automation.⁷ In this work, we have developed a reliable make-and-use flow system for the synthesis, analysis, and purification of isocyanides in regular laboratory practice. To demonstrate the utility of the approach, the reaction was applied to formamides bearing aromatic, aliphatic, and cyclic groups. The strategy described is one in which isocyanides are synthesized in flow mode and readily employed for post-modification reactions. This avoids the separation, purification, and storage of isocyanides and solves drawbacks of isocyanide chemistry including exposure to toxic and foul odour compounds and isocyanide decomposition. Despite some of the exemplified applications giving moderate to good yields, the designed flow set-up allows a facile access to valuable building blocks and could be important for the screening and discovery of bioactive molecules. Indeed, the system can be easily reconfigured to accommodate new reaction combinations. The complexity of the equipment described herein is one step away from automation and could be therefore further advanced depending on the laboratory capability and budget. Future efforts in this direction are ongoing in our laboratory and will be reported in due course.

Conflicts of interest

There are no conflicts to declare.

Notes and references

- For selected reviews, see: (a) C. Six and F. Richter, *Isocyanates*, Organic, in *Ullmann's Encyclopedia of Industrial Chemistry*, Wiley-VCH, Weinheim, Germany, 2003; (b) A.



- Dömling, *Chem. Rev.*, 2006, **106**, 17–89; (c) M. Suginome and Y. Ito, in *Science of Synthesis*, Thieme, Stuttgart, 2004, pp. 445–530; (d) M. A. Mironov, in *Isocyanide Chemistry*, Wiley-VCH, Weinheim, Germany, 2012, pp. 35–73; (e) A. Massarotti, F. Brunelli, S. Aprile, M. Giustiniano and G. C. Tron, *Chem. Rev.*, 2021, **121**, 10742–10788.
- (a) A. Dömling, *Comb. Chem. High Throughput Screening*, 1998, **1**, 1–22; (b) C. Hulme and T. Nixey, *Curr. Opin. Chem. Biol.*, 2003, **6**, 921–929; (c) A. Massarotti, F. Brunelli, S. Aprile, M. Giustiniano and G. C. Tron, *Chem. Rev.*, 2021, **121**, 10742–10788.
 - R. J. Slocombe, E. E. Hardy, J. H. Saunders and R. L. Jenkins, *J. Am. Chem. Soc.*, 1950, **72**, 1888–1891.
 - (a) A. Bonner, A. Loftus, A. C. Padgham and M. Baumann, *Org. Biomol. Chem.*, 2021, **19**, 7737–7753; (b) B. Gutmann, D. Cantillo and O. Kappe, *Am. Ethnol.*, 2015, **54**, 6688–6728.
 - L. Rogers and K. F. Jensen, *Green Chem.*, 2019, **21**, 3481–3498.
 - M. B. Plutschack, B. Pieber, K. Gilmore and P. H. Seeberger, *Chem. Rev.*, 2017, **117**, 11796–11893.
 - C. P. Breen, A. M. K. Nambiar, T. F. Jamison and K. F. Jensen, *Trends Chem.*, 2021, **3**, 373–386.
 - (a) S. Sharma, R. A. Maurya, K. Min, G. Y. Jeong and D. Kim, *Angew. Chem., Int. Ed.*, 2013, **52**, 7564–7568; (b) M. Baumann, A. M. Rodriguez Garcia and I. R. Baxendale, *Org. Biomol. Chem.*, 2015, **13**, 4231–4239.
 - P. Patil, M. Ahmadian-Moghaddam and A. Dömling, *Green Chem.*, 2020, **22**, 6902–6911.
 - K. A. Waibel, R. Nickisch, N. Möhl, R. Seimb and M. A. R. Meier, *Green Chem.*, 2020, **22**, 933–941.
 - Yield determination by ¹H-NMR analysis was unfeasible due to the overlap of phenyl proton signals with CHCl₃. The formation of phenylisocyanide (1f) was monitored by TLC analysis and quantified as reported in the ESI.
 - S. M. Creedon, H. K. Crowley and D. G. McCarthy, *J. Chem. Soc., Perkin Trans. 1*, 1998, 1015–1018.
 - K. Khamphaijun, P. Namnouad, A. Docker, A. Ruengsuk, J. Tantirungrotechai, R. D. Torres, D. J. Harding and T. Bunchuay, *Chem. Commun.*, 2022, **58**, 7253–7256.
 - T. Matsuo, A. Hayashi, M. Abe, T. Matsuda, Y. Hisaeda and T. Hayashi, *J. Am. Chem. Soc.*, 2009, **131**, 15124–15125.
 - For reviews on classical methods of preparing oxazoles, see: (a) I. J. Turchi, Oxazoles, in *Heterocyclic Compounds*, Wiley, New York, 1986, pp. 1–342; (b) F. W. Hartner, Oxazoles, in *Comprehensive Heterocyclic Chemistry II*, Pergamon Press, Oxford, 1996, p. 262, and references cited therein.
 - T. A. Rossa, N. S. Suveges, M. M. Sà, D. Cantillo and C. O. Kappe, *Beilstein J. Org. Chem.*, 2018, **14**, 506–514.
 - M. Baumann, I. R. Baxendale, S. V. Ley, C. D. Smith and G. K. Tranmer, *Org. Lett.*, 2006, **8**, 5213–5234.
 - R. Bossio, S. Marcaccini and R. Pepino, *Liebigs Ann. Chem.*, 1991, **10**, 1107–1108.
 - (a) L. Svec, L. Furiassi, C. G. Skibinski, T. M. Fan, G. J. Riggins and P. J. Hergenrother, *ACS Chem. Biol.*, 2018, **13**, 3206–3216; (b) J. Hergenrother, T. M. Fan and R. L. Svec, *US Pat.*, US20210002286, 2021.
 - (a) M. McLaughlin, R. M. Mohareb and H. Rapoport, *J. Org. Chem.*, 2003, **68**, 50–54; (b) C. E. Bell, A. Y. Shaw, F. De Moliner and C. Hulme, *Tetrahedron*, 2014, **70**, 54–59; (c) J. O. Strelnikova, N. V. Rostovskii, G. L. Starova, A. F. Khlebnikov and M. S. Novikov, *J. Org. Chem.*, 2018, **83**, 11232–11244; (d) C. H. Soh, W. K. Chui and Y. Lam, *J. Comb. Chem.*, 2006, **8**, 464–468; (e) X. Wang, J.-P. Fu, J.-H. Mo, Y.-H. Tian, C.-Y. Liu, H.-T. Tang, Z.-J. Sun and Y.-M. Pan, *Adv. Synth. Catal.*, 2021, **363**, 2762–2766.
 - R. Cannalire, C. Russo, B. Cerra, A. Gioiello, F. Brunelli, G. C. Tron and M. Giustiniano, *Mol. Diversity*, 2022, DOI: [10.1007/s11030-022-10418-4](https://doi.org/10.1007/s11030-022-10418-4).
 - (a) P. Josephson, V. Nykvist, W. Qasim, B. Blomkvist and P. Diner, *J. Chem. Educ.*, 2019, **96**, 1389–1394; (b) T. J. Reilly, *J. Chem. Educ.*, 1999, **76**, 1557.
 - A. Gioiello, A. Piccinno, A. M. Lozza and B. Cerra, *J. Med. Chem.*, 2020, **63**, 6624–6647.

