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COMMUNICATION

Accelerated Preparation of Pyridazines Enabled by High-Temperature Diazo Cycloadditions in Continuous Flow Mode

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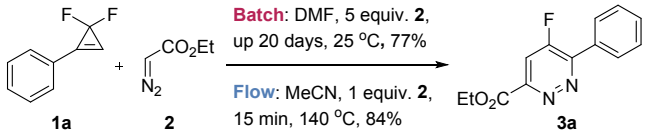
The effective application of continuous flow chemistry for the generation of substituted pyridazines *via* the thermal cycloaddition between α-diazo esters and difluorocyclopropenes is reported. Replacing DMF with MeCN and using stoichiometric reactant amounts at a temperature of up to 150 °C safely afforded the pyridazine targets in only 5-15 minutes in yields up to 93%.

Diazo compounds are well established reactive intermediates with widespread applications within modern synthetic chemistry.[1] However, their susceptibility to readily lose nitrogen gas in the presence of metals, acids, light or upon heating requires great caution when generating and employing these species. Most commonly diazo compounds are generated by oxidation of hydrazones,[2] *via* diazotisation of amines,[3] through diazo transfer using activated carbonyls,[4] or from bespoke precursors (e.g., *N*-nitroso-*N*-methylurea/MNU[5] or Diazald®[6] to generate diazomethane). Diazo compounds often serve as carbene precursors, and their value can be seen in their many uses in synthetic chemistry that typically involve insertion reactions (in C-H, N-H, O-H and S-H bonds) as well as addition reactions across π-bonds. To enable these transformations under milder conditions, transition metal catalysts based on rhodium or copper are frequently added which is accompanied by the loss of nitrogen gas.[7] Alternatively, photolysis of diazo species provides for a means to generate carbenes as well as ketenes allowing for many applications in target-oriented synthesis.[8] A further reactivity mode of diazo compounds is their ability to undergo dipolar cycloadditions affording a variety of valuable azaheterocycles.[9] However, in this case their limited stability must be carefully balanced with the need to overcome the energy barrier for such thermally driven reactions without triggering the loss of nitrogen gas. Therefore, cycloadditions utilising diazo compounds as dipoles can be sluggish and difficult to reproduce, especially when reaction scale-up is required.

Continuous flow chemistry[10] has frequently been employed when generating diazo compounds or triggering their onward reactions.[11] Miniaturisation is the key aspect of lab scale flow reactors that limits the amount of reactive species handled at any given time, whilst the improved heat and mass transfer of these set-ups mitigates safety risks by dissipating heat and releasing gaseous by-products in a controlled manner (i.e., using back-pressure regulators). Seminal reports highlight the use of flow technology for the safe preparation of diazomethane,[12] as well as the generation of stabilised and non-stabilised diazo compounds *via* oxidative means,[13] diazo transfer strategies[14] or *via* the photolysis of oxadiazolines.[15] This has also facilitated several important applications under thermal as well as photochemical conditions such as the Wolff rearrangement of diazo ketones,[16] the Arndt-Eistert homologation of carboxylic acids[17] and the Bamford–Stevens reaction.[18] While all these applications have in common that continuous flow processing facilitates the steady release of nitrogen gas using a back-pressure regulator, we noticed that related dipolar cycloadditions that retain the nitrogen unit of diazo compounds are underexplored despite the clear benefits of flow technology.



Scheme 1: Synthesis of fluoropyridazines *via* thermal [3+2] cycloaddition process in batch[19] and flow mode.

In this context we wished to explore the use of difluorocyclopropene derivatives as dipolarophiles in thermal

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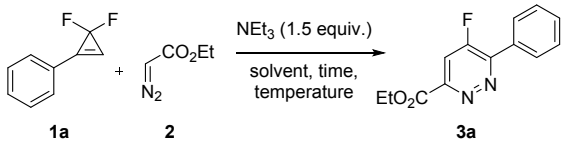
cycloaddition reactions with α-diazo esters. In a seminal study, Cossy and co-workers demonstrated this strategy for the assembly of medicinally relevant fluorinated pyridazines (Scheme 1).[19] While the overall strategy is very appealing, we noted several issues with the underlying process as this required the use of a 5-fold excess of the α-diazo ester species and the use of DMF (listed in the EU as a Substance of Very High Concern (SVHC)) as the reaction solvent. Moreover, this cycloaddition sequence required extended reaction times (typically 0.5-20 days at room temperature) as well as the exclusion of light and oxygen which taken altogether precludes its use outside academic labs. For several examples that failed to produce appreciable yields the authors noted a positive effect when increasing the reaction temperature up to 80 °C, nonetheless, the overall productivity remained low. Based on our experience in safely accelerating the generation of important heterocyclic scaffolds exploiting thermal flow processing[20] we wished to investigate its beneficial effect when generating drug-like pyridazines from α-diazo esters and difluorocyclopropenes in near-stoichiometric amounts.

We commenced our studies by evaluating the reaction between difluorocyclopropene **1** and ethyl diazoacetate in the presence of triethylamine (1.5 equiv.) as a scavenger for HF (Table 1). Adjustments from the reported batch procedure were made from the outset whereby the reaction mixture was kept under an atmosphere of nitrogen rather than argon, and the solvent was changed from DMF to MeCN due to the reproductive health hazards associated with the former. Moreover, we reduced the excess of ethyl diazoacetate from 5 equivalents to 2.3 equiv. in our initial trials.

Table 1: Initial trial reactions forming pyridazine **3a**.



1a **2** **3a**

	excess of **2**	time	solvent	temperature	yield
1[a,b]	5 equiv.	53 h	DMF	20 °C	77%
2[a,c]	2.3 equiv.	48 h	MeCN	20 °C	48%
3[c,d]	2.3 equiv.	3 h	MeCN	20 °C	19%
4[c,d]	1-5 equiv.	1 h	MeCN	20-50 °C	1-6%

[a]operated in batch; [b]argon atmosphere, [c]nitrogen atmosphere, [d]operated in (recirculating) flow mode.

As summarised in Table 1, the adjustments showed that the desired product is formed in an acceptable yield of 48% when operating this modified batch protocol for 48 hours (entry 2) which represents a 29% drop in yield compared to the reported batch conditions[19] (entry 1). The same conditions were subsequently employed when circulating the reaction mixture for 3 hours through a plug flow reactor (see ESI for details) giving a yield of 19%. While this represents a further drop in yield compared to the reported batch method, it indicated that these modifications (stoichiometry, solvent, N_2 atmosphere) allowed for the formation of pyridazine **3a** which despite the low yield gave a 17-fold improvement in productivity (product yield over reaction time). Several further modifications were made with a reduced residence time of 1 hour varying the temperature from 20°C to 50 °C and the stoichiometry from 1 to 5 equiv. ethyl diazoacetate, however, the yield of **3a** remained below 7% in all cases.

Next, the effect of further increasing reaction temperatures in flow mode was evaluated whilst retaining the use of only 1 equivalent of ethyl diazoacetate and shortening the residence time to 10 minutes, however, the yield of **3a** did not surpass 10% and large amounts of reactants along with some decomposed materials were observed (50-90 °C, Figure 1). Despite these setbacks, we next turned our attention to superheating the reaction mixture in flow mode which was facilitated by using a backpressure regulator set to 8 bar. This strategy would exploit the excellent heat transfer capabilities of the flow set-up whereby high spatiotemporal control would ensure that all reactants are subjected to the same residence time at these elevated temperatures up to 150 °C. Furthermore, the miniaturisation of the set-up ensures that the reaction safety is not compromised granting the operator access to process windows and reaction optimisation aspects that are not possible in batch mode. The upper temperature limit was set to 150 °C as above this value softening of the polymer tubing (PFA) may compromise the integrity and safety of the reactor set-up. Pleasingly, these changes were met with success when using a short residence time of only 5 minutes which was chosen to avoid competitive product degradation, affording good yields of almost 50% for product **3a** (Figure 1). Moreover, while increasing the temperature from 140 to 150 °C had little effect, passing the reaction mixture for a second time through the set-up at 140 °C (5 min) an increased yield of 62% was realised.

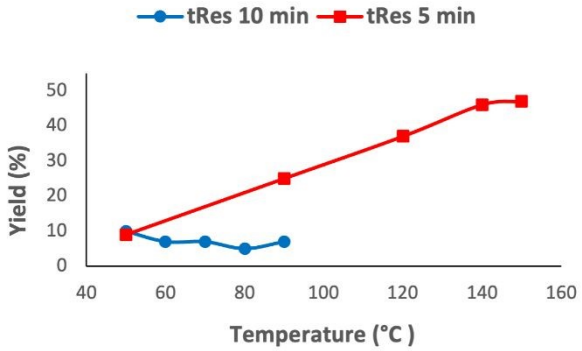
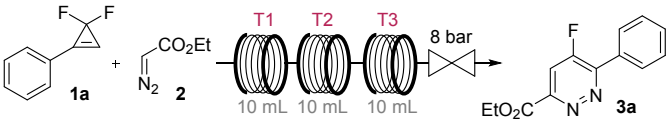


Figure 1: Yield of **3a** by varying reaction temperature using 1 equiv. of ethyl diazoacetate and MeCN as solvent.

Encouraged by these results, we studied the effect of residence time on product yield by passing the reaction mixture through a flow reactor set-up with larger coil volumes (i.e., 10, 20, 30 mL – all at 140 °C) which was accomplished by using multiple reactor coils of 10 mL volume in sequence. Higher flow rates would thereby be applied to achieve the same residence time (t_{Res}) when using a larger combined reactor volume which adds benefits by increasing mixing. As shown in Table 2, the enhanced mixing did indeed increase product formation for

analogous reactions with the same residence time (e.g., entry 1 vs 2 etc.) which amounted to up to 22% leading to the highest yield of 84% (entry 5 vs. 6) for fluoropyridazine target **3a**. Crucially, compared to the original batch protocol this surpasses not only reaction yield but also its productivity whilst ensuring safety through miniaturisation. The use of three reactor coils of 10 mL volume each also allowed us to study the effect of using a temperature gradient on the reaction performance, however, no clear trends were observed (entries 7-9) suggesting a consistent temperature of 140 °C is best.

Table 2: Screening of different residence times and temperature zones for the formation of pyridazine **3a**.

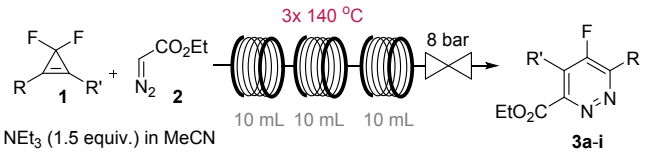


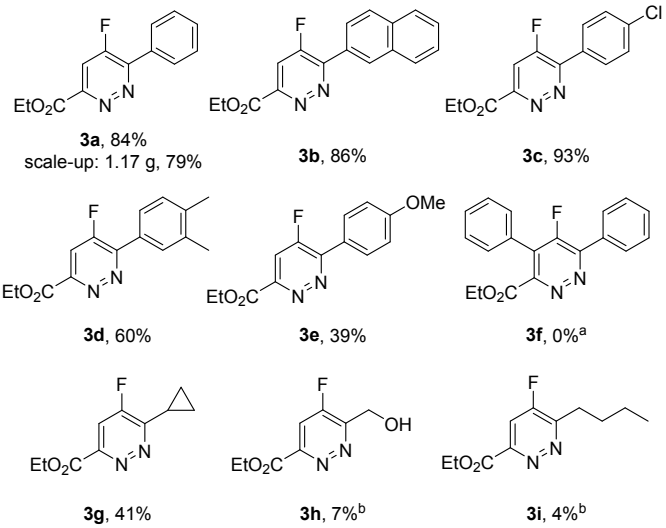
NEt_3 (1.5 equiv.) in MeCN

	T1 / T2 / T3			t_{Res} (coil volume)	yield and productivity
1	All at 140 °C			5 min (20 mL)	50% (6.0 mmol/h)
2	All at 140 °C			5 min (30 mL)	60% (7.2 mmol/h)
3	All at 140 °C			10 min (20 mL)	64% (3.8 mmol/h)
4	All at 140 °C			10 min (30 mL)	69% (4.6 mmol/h)
5	All at 140 °C			15 min (20 mL)	62% (2.5 mmol/h)
6	All at 140 °C			15 min (30 mL)	84% (3.4 mmol/h)
	Use of temperature gradient:				
	T1	**T2**	**T3**	t_{Res} (coil volume)	yield and productivity
7	100 °C	120 °C	140 °C	15 min (30 mL)	70% (2.8 mmol/h)
8	140 °C	120 °C	100 °C	15 min (30 mL)	69% (2.8 mmol/h)
9	120 °C	140 °C	120 °C	15 min (30 mL)	76% (3.0 mmol/h)

To investigate the generality of the optimised reaction conditions, a set of difluorocyclopropenes was prepared allowing us to study the effect of differently substituted aryl rings as well as alkyl moieties (see SI for full details). Pleasingly, it was found that several fluoropyridazine products were accessible in high yields when using the optimal conditions described above (140 °C, 15 min, 30 mL coil volume, 1.0 equiv. ethyl diazoacetate). The highest yields for further pyridazine products were observed when using a naphthyl substituent (**3b**) or a 4-chlorophenyl substituent (**3c**), whereas 3,4-dimethylphenyl (**3d**) and 4-methoxyphenyl (**3e**) provided acceptable yields (Scheme 2). Introducing two phenyl rings on the pyridazine scaffold by using the corresponding diphenyl-difluorocyclopropene was not successful highlighting the diminished reactivity of this sterically encumbered dipolarophile towards **3f**. At the same time, a cyclopropane moiety was tolerated despite the harsh reaction conditions which indicates the benefit of a short residence time when forming product **3g**. However, a butyl or hydroxymethyl side chain were problematic giving low yields of the corresponding products **3h** and **3i** along with substantial amounts of degradation products. Nonetheless, due to the continuous processing, small amounts of these targets could be generated that may find use in future medicinal chemistry efforts.

Moreover, the formation of pyridazine **3a** was scaled to 6 mmol affording 1.17 g of this product in a yield of 79% within a processing time of 25 minutes. With a productivity of 19 mmol/h, which represents a 65-fold increase from the original batch protocol, this clearly highlights how this flow process enables the safe generation of gram quantities of these densely functionalised pyridazines.





Scheme 2: Reaction scope under optimised conditions. [a] >90% of cyclopropene remaining; [b] >90% cyclopropene degradation.

In conclusion, this study describes the superior performance of a new high-temperature flow approach over an existing batch method for the cycloaddition between difluorocyclopropenes and ethyl diazoacetate furnishing versatile fluoropyridazines. Key targets such as the replacement of DMF with MeCN and the reduction of the excessive use of the hazardous diazo reactant were met as part of these efforts. Crucially, through miniaturisation flow processing provides for excellent heat transfer, spatiotemporal resolution as well as solvent superheating which grants a suitable process window to safely operate this process generating a set of synthetically valuable fluoropyridazine products. Intensification of the reaction

conditions in flow mode (i.e., t_{Res} = 5 min, T = 140 °C) leads to high productivity (up to 7.2 mmol/h) whilst significantly reducing side reactions as well as thermal runaway risks. Accessing these heterocyclic targets at gram scale was demonstrated highlighting the robustness and efficiency of the developed continuous method which lends itself towards further exploitations in industrial settings. Whilst flow-based diazo chemistry has previously been demonstrated for cases retaining the nitrogen unit within the product structure at ambient temperature, this work opens new avenues for powerful high-temperature applications that are expected to enable and impact the uptake of such methods in industry.

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Author contributions:

CRediT: **Jonathan Devlin** conceptualisation, formal analysis, investigation, methodology, writing – reviewing & editing; **Marcus Baumann** conceptualisation, funding acquisition, supervision, writing – original draft, reviewing & editing.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the ESI.

Notes and references

1 (a) G. Maas, *Angew. Chem., Int. Ed.*, 2009, **48**, 8186. (b) A. Ford, H. Miel, A. Ring, C. N. Slattery, A. R. Maguire and M. A. McKervey, *Chem. Rev.*, 2015, **115**, 9981.

2 (a) W. Liu, J. Twilton, B. Wei, M. Lee, M. N. Hopkins, J. Bacsa, S. S. Stahl and H. M. L. Davies, *ACS Catal.*, 2021, **11**, 2676. (b) H. Morrison, S. Danishefsky, and P. Yates, *J. Org. Chem.*, 1961, **26**, 2617. (c) T. L. Holton and H. Shechter, *J. Org. Chem.*, 1995, **60**, 4725. (d) M. I. Javed and M. Brewer, *Org. Lett.*, 2007, **9**, 1789.

3 (a) J. D. Clark, A. S. Shah and J. C. Peterson, *Thermochim. Acta*, 2002, **392–393**, 177. (b) J. D. Clark, J. D. Heise, A. S. Shah, J. C. Peterson, S. K. Chou, J. Levine, A. M. Karakas, Y. Ma, K.-Y. Ng, L. Patelis, J. R. Springer, D. R. Stano, R. H. Wettach and G. A. Dutra, *Org. Process Res. Dev.*, 2004, **8**, 176.

4 (a) J. S. Baum, D. A. Shook, H. M. L. Davies, and H. D. Smith, *Synth. Commun.*, 2006, **17**, 1709. (b) M. Regitz, *Angew. Chem., Int. Ed.*, 1967, **6**, 733.

5 (a) T. G. Archibald, J. C. Barnard, H. F. Reese (Aerojet), US Patent, 1998, US5854405. (b) E. Rossi, P. Woehl and M. Maggini, *Org. Process Res. Dev.*, 2012, **16**, 1146.

6 (a) T. J. de Boer and H. J. Backer, *Org. Synth.*, Coll. Vol. IV 1963, 250. (b) T. H. Black, *Aldrichimica Acta*, 1983, **16**, 3–10. (c) B. Morandi, and E. M. Carreira, *Science*, 2012, **335**, 1471. (d) R. A. Maurya, C. P. Park, J. H. Lee, and D.-P. Kim, *Angew. Chem., Int. Ed.,* 2011, **50**, 5952. (e) L. D. Proctor and A. J. Warr, *Org. Process Res. Dev.*, 2002, **6**, 884. (f) M. Struempel, B. Ondruschka, R. Daute and A. Stark, *Green Chem.*, 2008, **10**, 41.

7 (a) M. P. Doyle, R. Duffy, M. Ratnikov and L. Zhou, *Chem. Rev.*, 2010, **110**, 704. (b) H. M. L. Davies and R. E. J. Beckwith, *Chem. Rev.*, 2003, **103**, 2861.

8 (a) C. Empel, C. Pei and R. M. Koenigs, *Chem. Commun*., 2022, **58**, 2788. (b) R. D. C. Gallo, G. Cariello, T. A. C. Goulart and I. D. Jurberg, *Chem. Commun*., 2023, **59**, 734.

9 (a) M. Breugst, R. Huisgen and H.-U. Reissig, *Eur. J. Org. Chem.*, 2018, **2018**, 2477. (b) B. Gold, M. R. Aronoff and R. T. Raines, *Org. Lett.*, 2016, **18**, 4466. (c) X. Xu and M. P. Doyle, *Acc. Chem. Res.*, 2014, **47**, 4, 1396.

10 (a) B. J. Deadman, S. G. Collins and A. R. Maguire, *Chem. Eur. J.*, 2015, **21**, 2298. (b) M. Movsisyan, E. I. P. Delbeke, J. K. E. T. Berton, C. Battilocchio, S. V. Ley and C. V. Stevens, *Chem. Soc. Rev.*, 2016, **45**, 4892. (c) S. T. R. Müller and T. Wirth, *ChemSusChem*, 2015, **8**, 245.

11 B. J. Deadman, S. G. Collins and A. R. Maguire, *Chem. Eur. J.*, 2015, **21**, 2298.

12 (a) M. Struempel, B. Ondruschka and A. Stark, *Org. Process Res. Dev.,* 2009, **13**, 1014. (b) L. J. Martin, A. L. Marzinzik, S. V. Ley and I. R. Baxendale, *Org. Lett.*, 2011, **13**, 320. (c) E. Rossi, P. Woehl and M. Maggini, *Org. Process Res. Dev.*, 2012, **16**, 1146. (d) F. Mastronardi, B. Gutmann and C. O. Kappe, *Org. Lett.*, 2013, **15**, 5590.

13 D. N. Tran, C. Battilocchio, S.-B. Lou, J. M. Hawkins and S. V. Ley, *Chem. Sci.*, 2015, **6**, 1120.

14 (a) B. J. Deadman, R. M. O'Mahony, Denis Lynch, D. C. Crowley, S. G. Collins and A. R. Maguire, *Org. Biomol. Chem.*, 2016, **14**, 3423. (b) R. M. O'Mahony, D. Lynch, K. S. O'Callaghan, S. G. Collins and A. R. Maguire, *Org. Process Res. Dev.*, 2021, **25**, 2772.

15 A. Greb, J.-S. Poh, S. Greed, C. Battilocchio, P. Pasau, D. C. Blakemore and S. V. Ley, *Angew. Chem., Int. Ed.*, 2017, **56**, 16602.

16 (a) F. Minuto, A. Basso and M. Baumann, *J. Flow Chem.*, 2024, **14**, 615. (b) S. Fuse, Y. Otake and H. Nakamura, *Eur. J. Org. Chem*., 2017, **2017**, 6466. (c) A. I. Alfano, S. Pelliccia, G. Rossino, O. Chianese, V. Summa, S. Collina and M. Brindisi, *ACS Med. Chem. Lett.,* 2023, **14**, 672.

17 (a) V. V. Pendiukh, H. V. Yakovleva, I. A. Stadniy, O. Y. Pashenko, O. B. Volovenko, A. B. Rozhenko, S. V. Ryabukhin, D. M. Volochnyuk, *Org. Process Res. Dev.*, 2025, **29**, 6, 1476. (b) V. D. Pinho, B. Gutmann and C. O. Kappe, *RSC Adv.*, 2014, **4**, 37419.

18 H. E. Bartrum, D. C. Blakemore, C. J. Moody and C. J. Hayes, *Chem. Eur. J.*, 2011, **17**, 9586.

19 G. Tran, D. Gomez Pardo, T. Tsuchiya, S. Hillebrand, J.-P. Vors and J. Cossy, *Org. Lett.*, 2015, **17**, 3414.

20 (a) A. Bonner and M. Baumann, *Org. Biomol. Chem.*, 2024, **22**, 8323. (b) A. Bonner and M. Baumann, *Org. Process Res. Dev.*, 2023, **28**, 1567. (c) M. Duffy, M. Di Filippo and M. Baumann, *Tetrahedron Lett.*, 2021, **86**, 153522. (d) P. Naik, J. Garcia-Lacuna, P. O'Neill and M. Baumann, *Org. Process Res. Dev.*, 2023, **28**, 1587.

The data supporting this article have been included as part of the ESI.

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