COMMUNICATION

A Continuous Flow Synthesis of [1.1.1]Propellane and Bicyclo[1.1.1]pentane Derivatives

Kian Donnelly[a] and Marcus Baumann[a*]

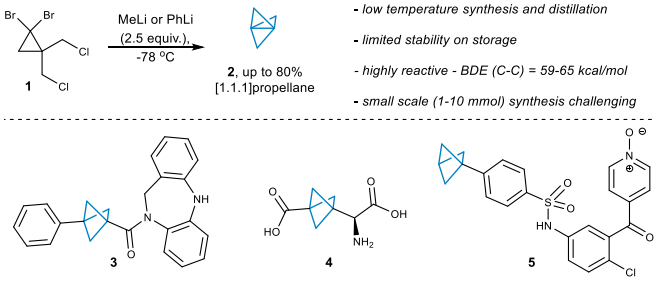
Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

A continuous flow process to generate [1.1.1]propellane on demand is presented rendering solutions of [1.1.1]propellane that can directly be derivatised into various bicyclo[1.1.1]pentane (BCP) species. This was realised in throughputs up to 8.5 mmol/h providing an attractive and straightforward access to gram quantities of selected BCP building blocks. Lastly, a continuous photochemical transformation of [1.1.1]propellane into valuable BCPs bearing mixed ester/acyl chloride moieties was developed.

Introduction

Bicyclo[1.1.1]pentane (BCP) derivatives have recently experienced a surge in interest due to their promising applications in biologically active compounds. The BCP motif can thereby act as an isostere for various functionalities such as para-substituted phenyl rings,[1-3] alkynyl[4] and *tert*-butyl groups[5] while offering the advantage of increased three-dimensionality which is becoming increasingly important in drug-discovery.[6]



Scheme 1. Synthesis of [1.1.1]propellane and selected BCPs.[2,5,7]

Despite recent advances in the synthesis of a range of BCP derivatives,[8] there remains a lack of methodology for providing facile access to this important motif. To date, the most commonly used method involves ring opening of [1.1.1]propellane,[9] which can be synthesised via cyclisation of tetrahalide **1** (Scheme 1).[10,11] While useful, this reaction requires the use of organometallic reagents and the resulting [1.1.1]propellane must be purified by vacuum distillation at low temperature. Additionally, [1.1.1]propellane must be stored in solution at low temperature to prevent decomposition via polymerisation or rearrangement to 3-methylenecylobutene.[12,13] The combination of these factors greatly affects the efficiency at which the desired BCP derivatives can be synthesised especially when small scale applications are targeted.

The use of flow chemistry offers many advantages over batch processing such as improved reaction control, due to increased heat and mass transfer, and increased safety due to contact with hazardous reagents being minimised.[14-16] In recent years, continuous flow technology has been widely adopted across academic and industrial laboratories for the synthesis of a range of compounds using organometallic reagents, allowing these reactions to be carried out on scale while eliminating common safety concerns associated with batch.[17,18] More importantly, the use of automated continuous flow platforms can result in much more efficient syntheses, with generally higher throughputs achieved than their batch counterparts.[19] Despite the advantages offered by continuous flow synthesis, and the increased interest in the synthesis of BCPs, no straightforward continuous flow process has been reported to date in the chemical literature[20] that enables the creation of [1.1.1]propellane at various scales. To overcome the common bottlenecks experienced in the synthesis of BCP derivatives, we envisioned the application of a continuous flow platform to the synthesis of [1.1.1]propellane. We anticipated that such a flow approach would allow for the effective on-demand synthesis of [1.1.1]propellane in a regular research laboratory, that could then be complemented by various functionalisation reactions in a streamlined manner, yielding valuable BCP derivatives without requiring to isolate and purify the highly reactive [1.1.1]propellane.

Results and Discussion

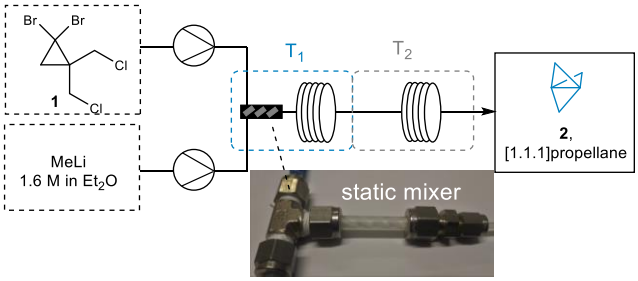
In order to set a benchmark with which our flow system would be compared, we first synthesised [1.1.1]propellane in batch mode using the method developed by Szeimies.[10,11] Specifically, we opted to use commercially available solutions of MeLi (1.6 M in Et_2O) and found the use of a rotary evaporator in combination with a dry-

[a] School of Chemistry, University College Dublin, Science Centre South, Belfield, D04 N2E2, Ireland.

Electronic Supplementary Information (ESI) available: Experimental procedures and copies of spectra. See DOI: 10.1039/x0xx00000x

ice/acetone cooling trap a practical solution to perform the isolation via distillation at low temperature.[21] This approach enabled the generation of [1.1.1]propellane from tetrahalide **1** in yields of 75-90% (established by ^{1}H-NMR), however, variations in yield were observed as a function of the scale, which encouraged us in our plan to transferring this reaction to continuous flow.

Next, we embarked on developing a continuous flow method for preparing solutions of [1.1.1]propellane in an analogous fashion. As depicted in Scheme 2, our initial flow setup consisted of two syringe pumps to combine a solution of substrate **1** with a stream of MeLi (1.6 M solution in Et_2O) via a 1/8" stainless steel T-piece. The use of syringe pumps allowed for accurate dosing of reagents, while maintaining a sealed system, preventing hydrolysis of methyl lithium. The reactor consists of PFA coils in two temperature zones, with cooling (T_1) being achieved using a commercially available Polar Bear Plus system, and after passing a segment of tubing at 25 °C (T_2) the reaction mixture is collected at 0 °C (flask in ice/water bath). Using this system, we initially experienced issues with frequent blocking due to the quantity of lithium salts produced. To overcome this, we utilised a wider bore T-piece (1/4") and incorporated a static mixer to increase turbulence.[22] The static mixer consisted of a Teflon helix housed within ¼" PFA tubing, which resulted in more efficient mixing, preventing the lithium salts from settling in the T-piece mixer.



Scheme 2: Continuous flow set-up.

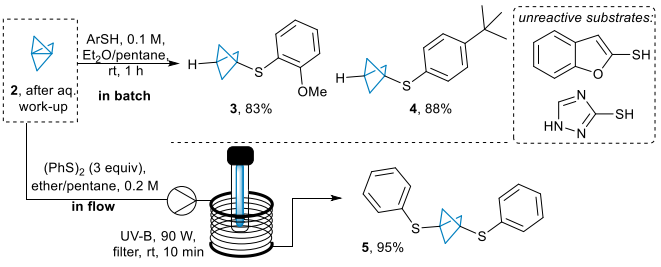
In order to determine the feasibility of avoiding the distillative work-up in favour of a simpler alternative, the collected reaction mixture was washed with water and the resulting organic phase was analysed by ^{1}H-NMR, using 1,3,5-trimethoxybenzene as an internal standard, for quantification. The replacement of vacuum distillation as a means of purification allowed for a simpler setup in addition to enabling rapid flow processing of material. Pleasingly, the results agreed with those of purification by distillation, and this method was used for quantifying reaction yields going forward. With issues relating to reactor fouling resolved, we began to optimise reaction conditions (Table 1). Firstly, a screen of commonly used solvents for this reaction was carried out (see Supporting Information), finding pentane and Et_2O to perform equally well, however, based on solubility of substrate **1**, pentane was chosen for further studies. Having established the optimal solvent, we proceeded to investigate the effect of residence time, stoichiometry and temperature. Similar to results from the batch test reactions, it was found that a slight excess of MeLi (2.2 equiv.) was sufficient to reliably achieve good conversion of substrate into product **2**. Interestingly, we found that an increased temperature for T_2 of 25 °C instead of 0 °C did not negatively affect conversion but rather increased the yield of **2** (Table 1, entries 3 & 4). In addition to avoiding blockages, shorter residence times (e.g. 3-6 min) were also found to increase yields. Further optimisation found that modifying stoichiometry by diluting the MeLi solution in place of adjusting flow rates resulted in higher yields and less incidences of fouling (entry 8). This is suspected to be due to retardation of the reaction taking place, resulting in salt formation occurring at a later stage in the reactor than previously observed. Consequently, a residence time of 6 minutes in combination with a reaction temperature of -15 °C (T1), followed by 25 °C (T_2) and a collection temperature of 0 °C were found best giving a yield of 50% for this continuous [1.1.1]propellane forming process.

Table 1: Optimisation of the flow synthesis of [1.1.1]propellane.

Entry	Conc. **1** [M]	MeLi equiv.	R_t [min][a]	T_1 [°C]	Yield [%][b]
1[c,e]	0.4	3.0	3.8	-10	19
2[c,f]	0.4	2.4	3.8	-15	30
3[c,e]	0.4	2.1	3.8	-10	19
4[c,f]	0.4	2.1	3.8	-10	27
5[c,f]	0.4	2.1	3.0	-15	28
6[c,f]	0.4	2.1	2.5	-15	15
7[d,f]	0.18	2.2	3.0	-15	27
8[d,f]	0.18	2.2	6.0	-15	50
9[d,f]	0.18	2.2	9.0	-15	40
10[d,f]	0.5	2.1	6.0	-15	27
11[d,f]	0.5	2.1	4.0	-15	30

[a] Reactor volume 6.8 mL; [b] ^{1}H-NMR yield; [c] Stoichiometry controlled using MeLi (1.6 M in Et_2O) at a reduced flow rate relative to **1**; [d] Stoichiometry controlled by diluting MeLi (1.6 M in Et_2O) to appropriate concentration. [e] T_2 = 0 °C; [f] T_2 = room temperature.

With optimised conditions in hand, we proceeded to demonstrate the utility of our continuous flow setup. To ensure that [1.1.1]propellane synthesised in this manner exhibited the same reactivity as that prepared via batch synthesis (purified by vacuum distillation), we wished to replicate some commonly used transformations. [1.1.1]Propellane is known to insert into S-H and S-S bonds[23,24] giving the resulting thioethers in high yields.

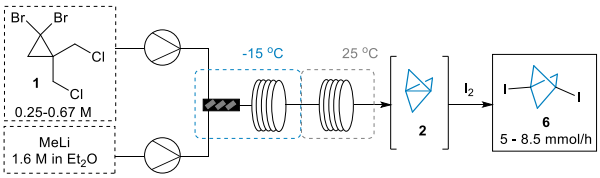


Scheme 3: Reaction of [1.1.1]propellane with thiols and disulfides.

The material generated by our flow platform and purified by aqueous extraction was thus reacted with some aryl thiols, affording the desired products in yields comparable to those of published

examples[24] (Scheme 3). Some unprecedented heterocyclic substrates including benzofurans and 1,2,4-triazoles unfortunately showed no reactivity under the conditions employed. Furthermore, reaction between [1.1.1]propellane and phenyl disulfide under continuous photochemical conditions rendered the expected product **5** in excellent yield.[23b]

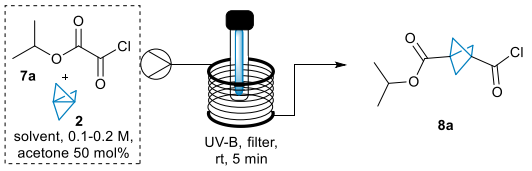
Encouraged by these results that showed that the [1.1.1]propellane generated in flow and purified by a simple extractive work-up, is producing known thioether adducts in excellent yields, we next turned our attention to evaluating the throughput and robustness of the initial flow process. Specifically, we wished to evaluate the synthesis of 1,3-diiodobicyclo[1.1.1]pentane (**6**, BCP-I_2), a commonly used building block exploited towards advanced BCP derivatives.[25,26] Initial attempts employing a high concentration of tetrahalide substrate **1** of 0.67 M provided a significant amount of product **6** when the [1.1.1]propellane solution obtained was quenched with iodine after aqueous work-up (Scheme 4). Despite the attractive throughput of 8.5 mmol/h (rendering 2.2 g of **6** in 50 minutes), the corresponding isolated yield of **6** was modest (25%) indicating degradation of [1.1.1]propellane under these conditions. To circumvent these issues, we next reduced the concentration of **1** to 0.25 M and upon reaching steady state operated the process for 40 minutes rendering 1.0 g (60%) of the target product **6** after isolation by trituration. This is equivalent to a throughput of 5 mmol/h (1.6 g/h) and demonstrates that our continuous process is effective in enabling the preparation of gram quantities of this valuable building block in a laboratory setting.



Scheme 4: Scale-up to generate 1,3-diiodobicyclo[1.1.1]pentane **6.**

In a final extension of our work we wished to evaluate the use of [1.1.1]propellane in light-mediated radical transformations[7, 23a, 24, 27, 28] where we were particularly interested in creating new C-C bonds. Specifically, we focused on studying the reaction of [1.1.1]propellane with 2-chloro-2-oxoacetates which are known to undergo radical mediated reactions when irradiated with light.[29] To the best of our knowledge, no detailed study of this reaction has been published to date.[30]

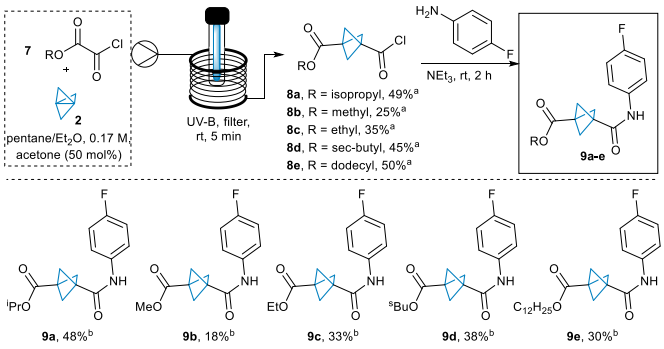
Isopropyl 2-chloro-2-oxoacetate **7a** was chosen as the model substrate that was mixed with a solution of [1.1.1]propellane in pentane/ether and subjected to irradiation using a Vapourtec UV-150 flow reactor equipped with a medium-pressure Hg-lamp (Scheme 5). Using this setup, we screened various conditions (see SI), firstly focusing on temperature, light source, and residence time. We soon found a short residence time (5 min) at room temperature to be best for this transformation. Interestingly, changing the medium-pressure Hg-lamp (90 W) to a low-power UV lamp (254 nm, 8 W) or a high-power LED lamp (365 nm, 50-100 W)[31] was determined to be detrimental to reactivity, however, introduction of a low-pass filter that excluded radiation above 400 nm was found to be beneficial. An excess of either starting material was found to decrease the yield.



Scheme 5: Photochemical flow reactor set-up.

Due to the requirement for [1.1.1]propellane to remain in a dilute solution changing the solvent from pentane/ether was not viable. Additionally, use of an ether-cosolvent did not increase conversion, but favoured side-product formation. Interestingly, we found that the presence of a small quantity of acetone resulted in increased yield. This was further investigated, and it was determined that 0.5 equivalents of acetone were the optimal quantity. It is hypothesised that this increase in yield may be due to a photosensitisation effect,[32] which is not observed at higher concentrations of acetone due to unwanted side reactions, which may include competing Norrish processes. A screen of some commonly used ketone-based photosensitisers was carried out including benzophenone, acetophenone and pinacolone, however, acetone remained the most efficient additive (see SI). It is worth noting that [1.1.1]propellane isolated after aqueous work-up did not perform as well as co-distilled material in this reaction, indicating the presence of impurities which are removed by distillation.

With the optimised conditions in hand the substrate scope of this reaction was investigated (Scheme 6). A range of alkyl esters were found to yield the desired BCP products, which still contained the acyl chloride moiety as a versatile functional handle. Substrates containing larger alkyl fragments generally resulted in higher yields, possibly due to their increased stability. Interestingly benzyl and propargyl substrates were not tolerated. Additionally, the presence of the chloro-oxoacetate moiety is crucial for reactivity, as the reaction did not proceed with dialkyl oxalates or amino-oxoacetyl chloride counterparts. Despite the moderate yields, this reaction allows for facile access to valuable building blocks, which have previously been accessible only through arduous multi-step modification of 1,3-diacetylbicyclo[1.1.1]pentane.[27,33] Treatment of the BCP acyl chloride intermediates (**8a-e**) with 4-fluoroaniline under standard amidation conditions subsequently rendered a selection of new BCP species **9a-e** bearing both an ester and an amide moiety (Scheme 6). This novel method thus offers an attractive entry to these valuable building blocks and compared to previously reported multi-step routes, our direct method provides these targets in high step- and atom-economy and additionally offers variation of the ester functionality without introducing additional synthetic steps.



Scheme 6: Synthesis of new BCP species ([a] ^{1}H-NMR; [b] isolated yield).

Conclusions

In conclusion, we have developed a continuous flow platform for the on-demand synthesis of [1.1.1]propellane. Crucially, this flow method bridges a gap as it allows to reliably execute this transformation on laboratory scale (1-10 mmol) whereas the related batch process is most effectively executed on larger scales to counteract product losses during the low-temperature distillation process as exemplified in recent industrial reports.[34] Applications to the synthesis of several important BCP derivatives are highlighted, including the multi gram-scale synthesis of BCP-I_2. Finally, we disclose the novel synthesis of a range of unsymmetrical BCP ester/amide structures which offers a more efficient and direct route to these valuable building blocks compared to previously published methods.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We are grateful to the School of Chemistry for providing a postgraduate scholarship (to KD). SFI is acknowledged for support through the 2018 Infrastructure Call (18/RI/5702) and the European Development Fund (12/RC2275_P2).

Notes and references

1 P. K. Mykhailiuk, *Org. Biomol. Chem.,* 2019, **17**, 2839.
2 R. Pellicciari, M. Raimondo, M. Marinozzi, B. Natalini, G. Costantino and C. Thomsen, *J. Med. Chem.,* 1996, **39**, 2874.
3 A. F. Stepan, C. Subramanyam, *et al.*, *J. Med. Chem.*, 2012, **55**, 3414.
4 I. S. Makarov, C. E. Brocklehurst, K. Karaghiosoff, G. Koch and P. Knochel, *Angew. Chem. Int. Ed.*, 2017, **56**, 12774.
5 M. V. West, J. Plancher, J. Gatfield and E. M. Carreira, *ChemMedChem*, 2015, **10**, 461.
6 F. Lovering, J. Bikker and C. Humblet, *J. Med. Chem.*, 2009, **52**, 6752.
7 X. Zhang, R. T. Smith, C. Le, S. J. McCarver, B. T. Shireman, N. I. Carruthers and D. W. C. MacMillan, *Nature*, 2020, **580**, 220.
8 (a) X. Ma and L. N. Pham, *Asian J. Org. Chem.*, 2020, **9**, 8; (b) M. M. D. Pramanik, H. Qian, W.-J. Xiao and J.-R. Chen, *Org. Chem. Front.*, 2020, **7**, 2531; (c) J. Kanazawa and M. Uchiyama, *Synlett*, 2019, **30**, 1.
9 A. M. Dimlaç, E. Spuling, A. de Meijere and S. Bräse, *Angew. Chem. Int. Ed.*, 2017, **56**, 5684.
10 K. Semmler, G. Szeimies and J. Belzner, *J. Am. Chem. Soc.*, 1985, **107**, 6410.
11 K. R. Mandanaro and W. P. Dailey, *Org. Synth.,* 1998, **75**, 98.
12 M. D. Levin, P. Kaszynski and J. Michl, *Chem. Rev.*, 2000, **100**, 169.
13 K. B. Wiberg and F. H. Walker, *J. Am. Chem. Soc.*, 1982, **104,** 5239.
14 (a) M. Baumann, T. S. Moody, M. Smyth and S. Wharry, *Org. Process Res. Dev.* 2020, **24**, 1802-1813; (b) M. B. Plutschack, B. Pieber, K. Gilmore and P. H. Seeberger, *Chem. Rev.*, 2017, **117**, 11796; (c) K. F. Jensen, *AIChE Journal*, 2017, **63**, 858.
15 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.
16 (a) M. Baumann, T. S. Moody, M. Smyth and S. Wharry, *Eur. J. Org. Chem.* 2020, 7398; (b) F. M. Akwi and P. Watts, *Chem. Commun.*, 2018, **54**, 13894.
17 (a) D. Dallinger, B. Gutmann and C. O. Kappe, *Acc. Chem. Res.* 2020, **53**, 1330; (b) L. Degennaro, C. Carlucci, S. De Angelis and R. Luisi, *J. Flow. Chem.*, 2016, **6**, 136; (c) B. Gutmann, C. O. Kappe, *J. Flow. Chem.* 2017, **7**, 65.
18 (a) B. Gutmann, D. Cantillo and C. O. Kappe, *Angew. Chem. Int. Ed.* 2015, **54**, 6688; (b) M. Colella, A. Nagaki and R. Luisi, *Chem. Eur. J.*, 2020, **26**, 19.
19 (a) A. Gioiello, A. Piccinno, A. M. Lozza, and B Cerra, *J. Med. Chem.*, 2020, **63**, 6624; (b) V. R. L. J. Bloemendal, M. A. C. H. Janssen, J. C. M. van Hest and Floris P. J. T. Rutjes, *React. Chem. Eng.*, 2020, **5**, 1186; (c) R. Porta, M. Benaglia and A. Puglisi, *Org. Process Res. Dev.*, 2016, **20**, 2.
20 The patent literature lists one recent continuous method for generating [1.1.1]propellane, for details please see: K. D. Bunker *et al.*, WO 2019/051038 A1 (Mar 14, 2019).
21 R. Gianatassio, J. M. Lopchuk, J. Wang, C.-M. Pan, L. R. Malins, L. Prieto, T. A. Brandt, M. R. Collins, G. M. Gallego, N. W. Sach, J. E. Spangler, H. Zhu, J. Zhu and P. S. Baran, *Science,* 2016, **351**, 241.
22 A. Ghanem, T. Lemenand, D. Della Valle and H. Peerhossaini, *Chem. Eng. Res. Des.*, 2014, **92**, 205.
23 (a) R. M. Bär, S. Kirschner, M. Nieger and S. Bräse, *Chem. Eur. J.*, 2018, **24**, 1373; (b) R. M. Bär, G. Heinrich, M. Nieger, O. Fuhr and S. Bräse, *Beilstein J. Org. Chem.* 2019, **15**, 1172.
24 K. B. Wiberg and S. T. Waddell, *J. Am. Chem. Soc.*, 1990, **112**, 2194.
25 Y. L. Goh, E. K. W. Tam, P. H. Bernardo, C. B. Cheong, C. W. Johannes, A. D. William and V. A. Adsool, *Org. Lett.*, 2014, **16**, 1884.
26 K. B. Wiberg and N. McMurdle, *J. Am. Chem. Soc.*, 1994, **116**, 11990.
27 P. Kaszynski and J. Michl, *J. Org. Chem.*, 1988, **53**, 4593.
28 J. Nugent, C. Arroniz, B. R. Shire, *et al.*, *ACS Catal.*, 2019, **9**, 9568.
29 S. Kim and S. Y. Jon, *Tetrahedron Lett.*, 1998, **39**, 7317.
30 For an example amongst patents: Y. Suzuki, D. Jimenez-Teja, C. Salomé, T. Fessard, WO 2017/157932 A1 (Sep 21, 2017).
31 For recently published examples from our lab using this high-power LED lamp, please see: (a) S. Bonciolini, M. Di Filippo and M. Baumann, *Org. Biomol. Chem.*, 2020, **18**, 9428; (b) M. Di Filippo and M. Baumann, *Eur. J. Org. Chem.*, 2020, **39**, 6199.
32 C. Michelin and N. Hoffmann, *ACS Catal.*, 2018, **8**, 12046.
33 S. O. Kokhan, Y. B. Valter, A. V. Tymtsunik, I. V. Komarov and O. O. Grygorenko, *Eur. J. Org. Chem.*, 2017, **43**, 6450.
34 C. Zarate, M. Ardolino, *et al.*, *Org. Process Res. Dev.* 2020; doi.org/10.1021/acs.oprd.0c00446

