Green Chemistry

PAPER



Cite this: *Green Chem.*, 2018, **20**, 3134

# Sequential (3 + 2) cycloaddition and (5 + *n*) annulation for modular synthesis of dihydrobenzoxazines, tetrahydrobenzoxazepines and tetrahydrobenzoxazocines†

Alex Muthengi,[a] Xiaofeng Zhang,[a] Gagan Dhawan,[b] Wensheng Zhang,[c] Francesca Corsini[a] and Wei Zhang *[a]

Received 8th April 2018,
Accepted 11th June 2018

DOI: 10.1039/c8gc01099d

rsc.li/greenchem

A two-step method for the (3 + 2) cycloaddition of azomethine ylides followed by a double $S_N2$ substitution-based (5 + *n*) annulation is introduced for the modular synthesis of dihydrobenzoxazine, tetrahydrobenzoxazepine and tetrahydrobenzoxazocine derivatives. After a quick water wash without further purification, the (3 + 2) cycloaddition intermediates were used for the (5 + *n*) annulation to afford products. Green chemistry metrics analysis of the synthetic processes provided favorable results.

## Introduction

Dihydrobenzoxazine, tetrahydrobenzoxazepine and tetrahydrobenzoxazocine are privileged heterocyclic ring systems which can be found in many biologically active compounds such as dihydrobenzoxazine-bearing benoxacor **A**,[1] levofloxacin **B**[2] and URAT-1 inhibitor **C**;[3] tetrahydrobenzoxazepine-bearing CBP bromodomain inhibitor TPOP146 **D**,[4] kinase and mTOR inhibitor **E**[5] and anti-tumor agent **F**;[6] and tetrahydrobenzoxazocine-bearing Nefopam **G**[7] and hepatitis C virus inhibitor **H** (Fig. 1).[8]

Reported methods for the synthesis of dihydrobenzoxazine scaffold include cross-coupling and aromatization reactions[9] and (3 + 3) cycloaddition of azomethine ylides with quinine monoimides (Scheme 1A).[10] Methods for tetrahydrobenzoxazepine and tetrahydrobenzoxazocine ring systems require multi-step synthesis.[11] For example, the Knapp group reported a five-step synthesis of tetrahydrobenzoxazepines through reductive amination, Boc protection, cyclization, deprotection and reduction (Scheme 1B).[4] The Naganathan group assembled a tetrahydrobenzoxazepine scaffold in five steps for synthesis of kinase and mTOR inhibitor **E**.[5] The Narjes group reported the synthesis of tetrahydrobenzoxazocine derivatives in more than six reaction steps (Scheme 1C).[8] The Ramachary group reported a three-step synthesis of Nefopan analogues through cascade enamine amination/isoaromatization/allylation and ring closing metathesis (Scheme 1D).[12] The (3 + 2) cycloaddition, also called 1,3-dipolar cycloaddition, was discovered

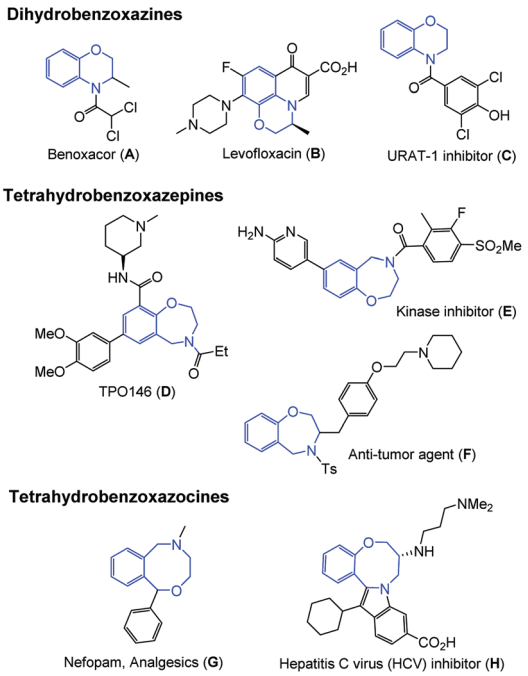
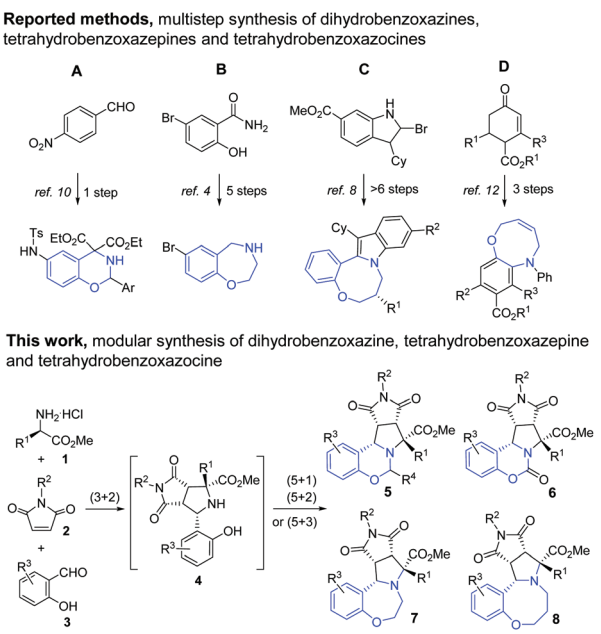



**Fig. 1** Biologically active compounds bearing dihydrobenzoxazine, tetrahydrobenzoxazepine and tetrahydrobenzoxazocine scaffolds.

[a]*Department of Chemistry and Centre for Green Chemistry, University of Massachusetts Boston, 100 Morrissey Boulevard, Boston, MA 02125, USA. E-mail: wei2.zhang@umb.edu*
[b]*Department of Biomedical Science, Acharya Narendra Dev College, University of Delhi, New Delhi-110019, India*
[c]*School of Science and Technology, Jiaozuo Teachers College, Jiaozuo 454100, China*
†Electronic supplementary information (ESI) available: Detailed experimental procedures, compound characterization, NMR spectra, green chemistry metrics analysis. See DOI: 10.1039/c8gc01099d




**Scheme 1** Methods for the synthesis of dihydrobenzoxazines, tetrahydrobenzoxazepines and tetrahydrobenzoxazocines.

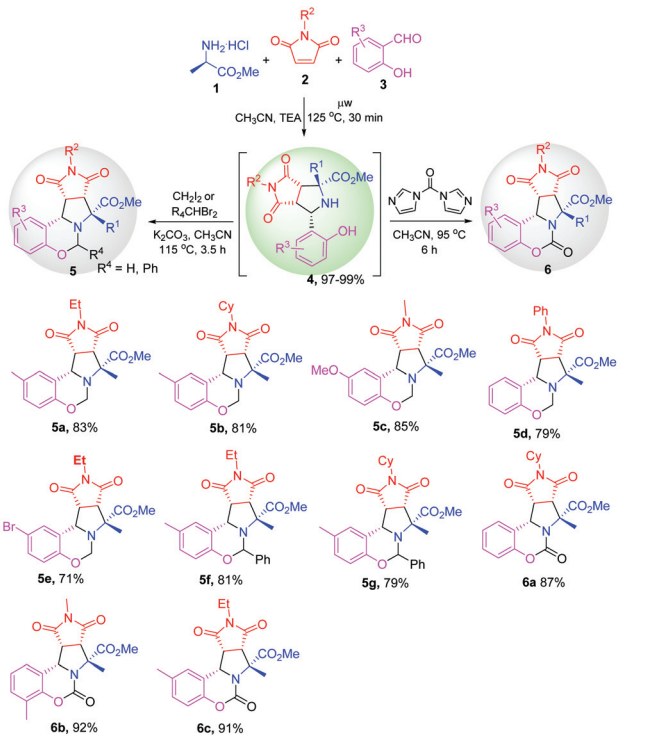
by Rolf Huisgen in 1960s. He synthesized 1,2,3-triazole using an organic azide and an alkyne.[13]

In recent years, our lab has developed a series of step- and atom-economic synthesis for heterocyclic systems,[14] with a special effort on the (3 + 2) cycloaddition-initiated reaction sequences.[15] Introduced in this paper is a new sequence involving (3 + 2) cycloaddition followed by double $S_N2$ substitution-based (5 + *n*) annulation for modular synthesis of dihydrobenzoxazines **5** and **6**, tetrahydrobenzoxazepines **7** and tetrahydrobenzoxazocines **8** (Scheme 1). The common intermediates **4** resulted from the (3 + 2) cycloaddition were used for the post-condensation reactions to form six-, seven-, and eight-membered ring scaffolds **5–8**.

## Results and discussion

Three-component (3 + 2) cycloadditions of amino esters **1**, malemides **2** and benzaldehydes adduct **3** have been well-established for diastereoselective synthesis of proline esters **4**.[15,16] We designed a modular approach to conduct the post-condensation reactions of **4** for (5 + 1), (5 + 2) and (5 + 3) annulations through double $S_N2$ reactions for the synthesis of dihydrobenzoxazines **5** and **6**, tetrahydrobenzoxazepines **7** and tetrahydrobenzoxazocines **8**. We first explored the (3 + 2) cycloaddition and the (5 + 1) annulation sequence. After screening the reaction conditions, it was found that reaction of **4** (1 equiv.), diiodomethane or dibromoalkane (2.0 equiv.) and $K_2CO_3$ (2.5 equiv.) at 115 °C in a sealed vial for 3.5 h gave compounds **5a–5e** in 71–85% yields (Table 1). Using dibromomethyl benzene as an electrophile gave **5f** and **5g** in 81% and 79% yields, respectively as the major diastereomers (see the ESI†).

**Table 1** Two-step (3 + 2) cycloaddition and (5 + 1) annulation reactions[a,b]

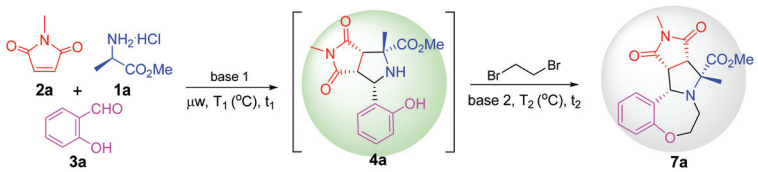



[a] Reaction conditions for **5**: (3 + 2) cycloaddition adduct **4** (1 equiv.), dibromomethane/diiodomethane, (dibromomethyl)benzene (2 equiv.) and $K_2CO_3$ (2.5 equiv.); Reaction conditions for **6**:**4** (1 equiv.), 1,1′-carbonyldiimidazole (1.5 equiv.). [b] Isolated yield for the (5 + 1) annulation.

We then extended the (5 + 1) annulation reactions using 1,1′-carbonyldiimidazole (1.5 equiv.) as an electrophile. The reactions completed in 6 h at 95 °C to give **6a**, **6b** and **6c** in 87%, 92% and 91% yields, respectively (Table 1). It is noteworthy that products **6a–6c** were precipitated out from the reaction mixtures without further purification.

After successfully conducted the (3 + 2) cycloaddition and (5 + 1) annulation reactions for dihydrobenzoxazines **5** and **6**, we next explored the (3 + 2) cycloaddition and (5 + 2) annulation reactions for tetrahydrobenzoxazepines **7**. D-Alanine methyl ester **1a**, *N*-methylmaleimide **2a**, and salicylaldehyde **3a** were used as model compounds for the development of reaction conditions (Table 2). After screening of solvents, bases, reaction temperature and time, it was found that 1.2 : 1.1 : 1 of D-alanine methyl ester **1a**, *N*-methylmaleimide **2a** and salicylaldehyde **3a** respectively, using $Et_3N$ as a base and MeCN as a solvent, under microwave heating at 125 °C for 30 min gave **4a** in 97% LC yield and high diastereoselectivity of 39 : 1 dr (Table 2, entry 3). A control experiment for (3 + 2) cycloaddition under conventional heating revealed it needed 2 h to complete the reaction (Table 2, entry 12). The reaction mixture containing compound **4a** was washed with 1 mL of $H_2O$ to remove $Et_3N$ and then used for the (5 + 2) annulation reaction by adding 2 equiv. of 1,2-dibromoethane and 2.5 equiv. of

Table 2 Optimization of (3 + 2) cycloaddition and (5 + 2) annulation reactions[a]



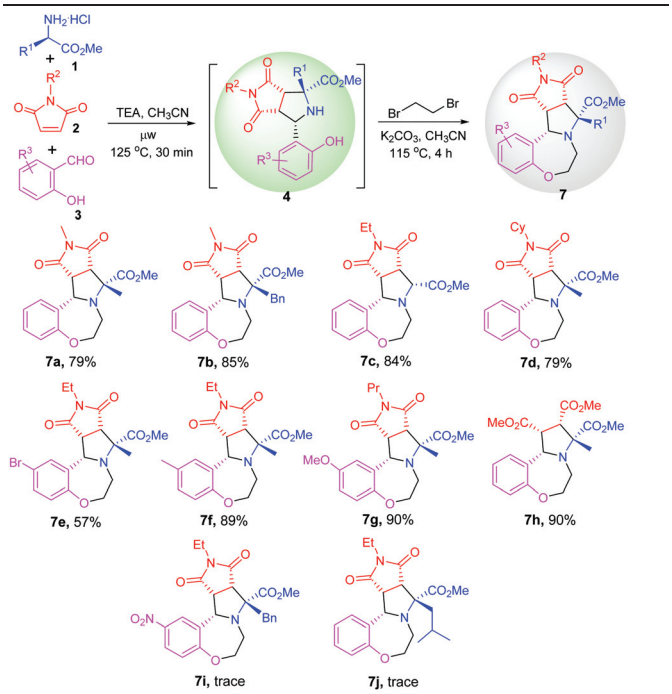

| Entry | $T1$ (°C) | Solvent | Base 1 (2 eq.) | $t_1$ (min) | **4a**[b] (%) | **4a** dr | $T2$ (°C) | $t_2$ (h) | Base 2 (2.5 eq.) | **7a**[b] (%) | **7a** dr |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 115 | ACN | TEA | 20 | 81 | 27 : 1 | 100 | 2 | $K_2CO_3$ | 31 | 17 : 1 |
| 2 | 125 | ACN | TEA | 25 | 93 | 32 : 1 | 110 | 2 | $K_2CO_3$ | 45 | 19 : 1 |
| 3 | 125 | ACN | TEA | 30 | 97 | 39 : 1 | 110 | 3 | $K_2CO_3$ | 69 | 21 : 1 |
| 4 | 125 | ACN | DIPEA | 30 | 92 | 36 : 1 | 110 | 3 | TEA | 0 | — |
| 5 | 125 | ACN | TEA | 30 | 97 | 39 : 1 | 115 | 3 | $K_2CO_3$ | 75 | 29 : 1 |
| **6** | **125** | **ACN** | **TEA** | **30** | **97** | **39 : 1** | **115** | **4** | **$K_2CO_3$** | **88 (79)**[c] | **37 : 1** |
| 7 | 125 | ACN | TEA | 30 | 97 | 39 : 1 | 115 (μw) | 0.5 | $K_2CO_3$ | Trace | — |
| 8 | 125 | PhMe | TEA | 30 | 93 | 37 : 1 | 120 | 3 | $K_2CO_3$ | 80 | 32 : 1 |
| 9 | 130 | ACN | $K_2CO_3$ | 30 | 82 | 15 : 1 | 120 | 4 | $K_2CO_3$ | 88 | 37 : 1 |
| 10 | 125 | PhMe | $K_2CO_3$ | 30 | 84 | 29 : 1 | 115 | 5 | $K_2CO_3$ | 88 | 37 : 1 |
| 11 | 125 | ACN | $K_2CO_3$ | 30 | 79 | 17 : 1 | 110 | 3 | DIPEA | 0 | — |
| 12[d] | 125 | ACN | TEA | 2 h | 97 | 39 : 1 | — | — | — | — | — |

[a] Reaction conditions: D-Alanine methyl ester **1a** (1.2 equiv.), *N*-methylmaleimide **2a** (1.1 equiv.), salicylaldehyde **3a** (1 equiv.) and $Et_3N$ (2 equiv.) under microwave heating for **4a**, then 1 : 2 : 2.5 of **4a** : $BrCH_2CH_2Br$ : $K_2CO_3$ under conventional heating. [b] Detected by LC-MS. [c] Isolated yield. [d] Contol reaction using conventional heating.

$K_2CO_3$ as a base. After conventional heating at 110 °C for 3 h, the (5 + 2) annulation product **7a** was obtained in 69% LC yield (Table 2, entry 3). Microwave heating was found not good for the step of (5 + 2) annulation (Table 2, entry 7). Further optimization of the (5 + 2) annulation conditions revealed that 2 equiv. of 1,2-dibromoethane and 2.5 equiv. of $K_2CO_3$ at 115 °C under 4 h conventional heating was the optimized conditions which gave **7a** in 88% LC yield and 37 : 1 dr (Table 2, entry 6). It was found that $Et_3N$ and DIPEA could be used for the (3 + 2) cycloaddition, but they were not suitable for the (5 + 2) annulation (Table 2, entries 4 and 11). Since the (3 + 2) cycloaddition was highly diastereoselective, compound **7a** was isolated as a single diastereomer.

Under the optimized conditions for sequential (3 + 2) cycloaddition and (5 + 2) annulation reactions, the synthesis of 10 analogues of tetrahydrobenzoxazepines **7a–7j** were conducted using different amino esters ($R^1$ = H, Me, Bn, i-Bu), maleimides ($R^2$ = Me, Et, Pr, *c*-$C_6H_{11}$), and salicyladehydes ($R^3$ = H, Br, Me, OMe, $NO_2$) (Table 3). The reactions of four different maleimides with amino esters ($R^1$ = Me or Bn) and salicylaldehydes ($R^3$ = H, 5-Me, 5-OMe) gave **7a–7g** in 57–90% yields (Table 3). The reaction of *E*-dimethyl fumarate instead of maleimides gave product **7h** as a single diastereomer in 90% yield (see the ESI†). The stereochemistry result was similar to that in our previous report.[15d] For salicyladehydes, the presence of electron withdrawing groups like 5-Br as $R^3$ led to product **7e** in a reduced yield of 57%. The IR spectrum of the undesired product **7e′** had a strong –OH stretching peak at around 3339 $cm^{-1}$. $^1$H-NMR and $^{13}$C-NMR analyses also indicated that **7e′** is a mono $S_N2$ reaction product (see the ESI†). This is probably due to the bromo on the phenyl ring deactivated the second $S_N2$ reaction of the hydroxyl group. In other reactions,

Table 3 Two-step (3 + 2) cycloaddition and (5 + 2) annulation reactions[a]



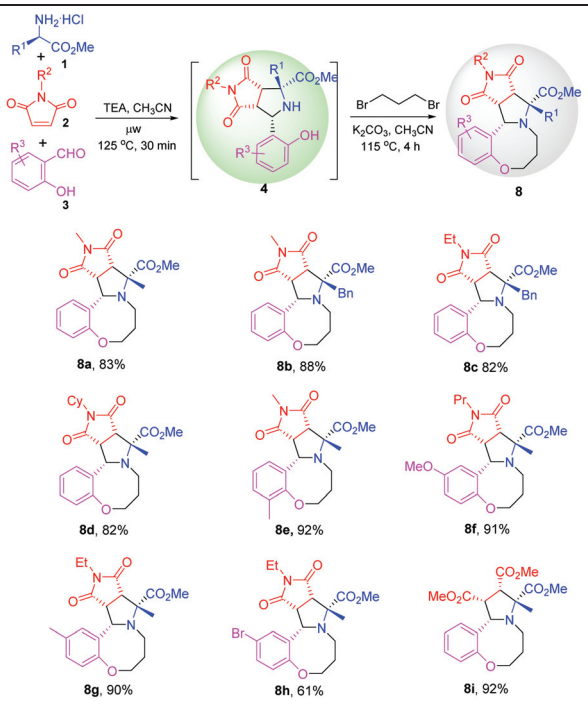

[a] Reaction conditions: Amino ester **1** (1.2 equiv.), maleimide or *E*-dimethyl fumarate **2a** (1.1 equiv.), salicylaldehyde **3** (1 equiv.) and $Et_3N$ (2 equiv.) in MeCN, microwave heating for 30 min for **4**, then 1 : 2 : 2.5 of **4** : 1,2-dibromoethane : $K_2CO_3$ in MeCN, thermal heating at 115 °C for 4 h, isolated yield.

amino esters bearing H or Me as $R^1$ groups gave products **7a–7h** in good yields. However, amino esters with Bn and i-Bu only gave trace amount of products **7i** and **7j** as observed on the LC-MS (see the ESI†). This is due to the steric hindrance of the bulky Bn and i-Bu groups blocking the second $S_N2$ reaction and only resulted mono $S_N2$ reaction products.

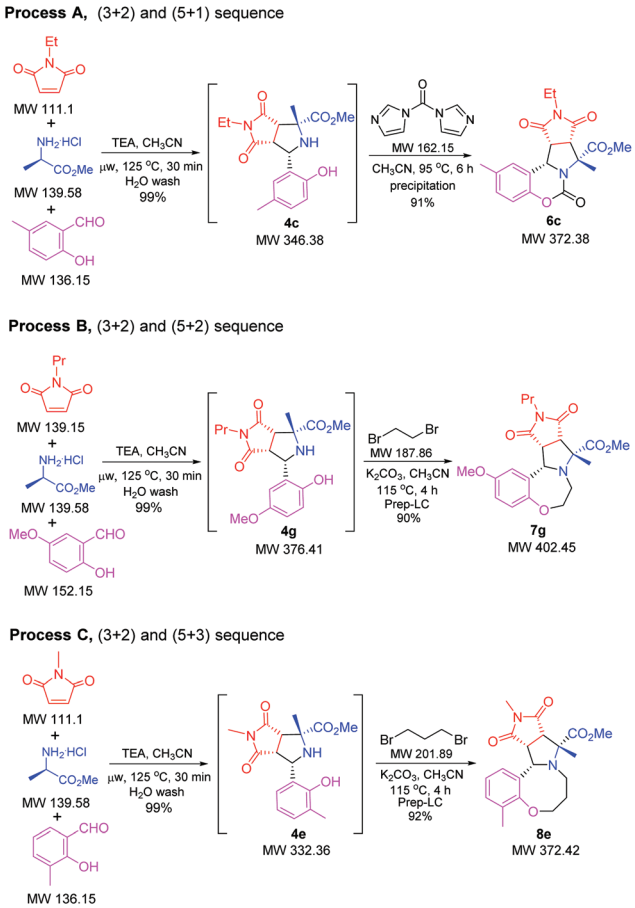
The reaction conditions developed for the (3 + 2) cycloaddition and (5 + 2) annulation sequence was readily applied to the (3 + 2) cycloaddition and (5 + 3) annulation sequence for making tetrahydrobenzoxazocines **8**. By using 1,3-dibromopropane as an electrophile for (5 + 3) annulations, a series of nine tetrahydrobenzoxazocine analogues **8a–8i** were synthesized in 61–92% yields (Table 4). Maleimides with Me, Et, Pr and *c*-$C_6H_{11}$ as $R^2$ had no significant impact on the product yields. But the $R^3$ of salicyladehydes had a significant impact. Salicyladehydes with electron-donating groups such as 5-OMe, 5-Me and 3-Me gave **8e–8g** > 90% yields, whereas salicylaldehydes with electron-deficient 5-Br gave **8h** in 61% yield. The reaction of *E*-dimethyl fumarate afforded product **8i** as a single diastereomer in 92% yield.

To evaluate the greenness of the sequential (3 + 2) cycloaddition and (5 + *n*) annulations processes A, B and C shown in Scheme 2, a series of green metrics calculations were conducted which include atom economy (AE), atom efficiency (AEf), carbon efficiency (CE), reaction mass efficiency (RME),

**Table 4** Two-step (3 + 2) cycloaddition and (5 + 3) annulation reactions[a]




[a] Reaction conditions: Amino ester **1** (1.2 equiv.), maleimide or *E*-dimethyl fumarate **2a** (1.1 equiv.), salicylaldehyde **3** (1 equiv.) and $Et_3N$ (2 equiv.) in MeCN, microwave heating for 30 min for **4**, then 1 : 2 : 2.5 of **4** : 1,3-dibromopropane : $K_2CO_3$ in MeCN at 115 °C for 4 h, isolated yield.



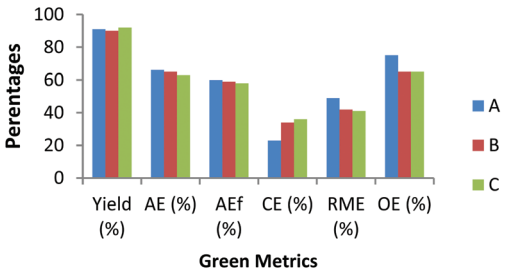

**Scheme 2** Processes A, B & C for green metrics analysis.

optimum efficiency (OE), process mass intensity (PMI), *E*-factor (*E*), solvent intensity (SI), and water intensity (WI) (see ESI† for definition of metrics and detailed calculations).[17–19] The AE for processes A, B and C were 66%, 65% and 63%, respectively (Table 5). This was less than 100% due to the formation of by-products: two molecules of imidazole for process A, and two molecules of HBr for processes B and C. The CE, RME and OE for process A, were 23%, 49% and 75%, while process B had 34%, 42% and 65%, and process C had 36%, 41%, and 65% respectively. RME is one of the most useful metric to determine the greenness of the process, since it takes into account the reactant mass, yield and atom economy. RME for processes A, B and C were 49%, 42% and 41%, respectively. Product **6c** from process A was purified by simple precipitation, while **7g** and **8e** for processes B and C were purified by Angela HP-100 prep-LC system. The optimum efficiency (OE) for processes A (75%), B (65%) and C (65%) were high.

The lower the process mass intensity (PMI) the better the process. The PMI for processes A (43), B (40) and C (41) were lower hence efficient (Table 6). It has been shown that solvents constitute 80–90% of the mass intensity of a pharmaceutical process manufactured in a batch operation, and 50% of greenhouse gas emissions.[18] Therefore, solvent intensity (SI) and water intensity (WI) values were calculated. The solvent inten-

Table 5 Green metrics (AE, AEF, CE, RME, OE and MP) for processes A–C

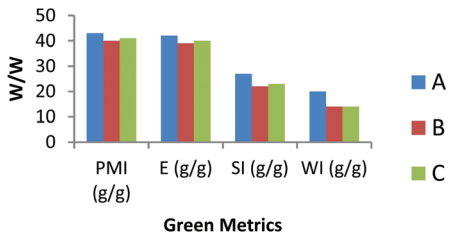
| Process | Isolation steps | Yield (%) | AE (%) | AEf (%) | CE (%) | RME (%) | OE (%) |
|---|---|---|---|---|---|---|---|
| A | 1 | 91 | 66 | 60 | 23 | 49 | 75 |
| B | 1 | 90 | 65 | 59 | 34 | 42 | 65 |
| C | 1 | 92 | 63 | 58 | 36 | 41 | 65 |




The higher the value (closer to 100%), the greener the reaction process.

Table 6 Green metrics (PMI, *E*-factor, SI, and WI) for processes A–C

| Process | PMI (g g$^{-1}$) | *E* (g g$^{-1}$) | SI (g g$^{-1}$) | WI (g g$^{-1}$) |
|---|---|---|---|---|
| A | 43 | 42 | 27 | 20 |
| B | 40 | 39 | 22 | 14 |
| C | 41 | 40 | 23 | 14 |




The lower the value, the better the reaction process.

sity (SI) for processes A, B and C were 27, 22 and 23 respectively. Similarly, the water intensity (WI) for process A (20), and 14 for both processes B and C were lower. Therefore, the three processes were efficient since less solvents including water were used.

## Conclusions

We have developed a sequential (3 + 2) cycloaddition of azomethine ylides followed by (5 + *n*) annulation for modular synthesis of six-, seven- and eight-membered dihydrobenzoxazines, tetrahydrobenzoxazepines and tetrahydrobenzoxazocines, respectively. This two-step synthesis is diastereoselective and highly efficient. The atom- and step-economy were obtained from the three-component (3 + 2) cycloadditions and the sequential double $S_N2$ substitutions. The intermediates from the (3 + 2) cycloadditions were quickly washed with water to remove the base and then used for the (5 + *n*) annulations. The (5 + 1) annulation products were purified by precipitation or flash chromatography, while the (5 + 2) and (5 + 3) annulation products were purified by flash chromatography or prep-LC. A series of green chemistry metrics analysis for the reaction processes was performed and provided favourable results.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

This work was supported by the Centre for Green Chemistry of UMass Boston. GD wishes to gratefully acknowledge University Grants Commission of India for the award of UGC-Raman Fellowship.

## Notes and references

1 L. Scarponi and D. D. Buono, *J. Agric. Food Chem.*, 2005, **53**, 2483–2488.
2 (*a*) L. A. Mitscher, *Chem. Rev.*, 2005, **105**, 559–592; (*b*) J. F. Bower, P. Szeto and T. Gallagher, *Org. Lett.*, 2007, **9**, 3283–3286.
3 L. Bagnoli, S. Casini, F. Marini, C. Santi and L. Testaferri, *Tetrahedron*, 2013, **69**, 481–486.
4 T. A. Popp, C. Tallant, C. Rogers, O. Fedorov, P. E. Brennan, S. Muller, S. Knapp and F. Bracher, *J. Med. Chem.*, 2016, **59**, 8889–8912.
5 S. Naganathan, D. L. Andersen, N. G. Andersen, S. Lau, A. Lohse and M. D. Sørensen, *Org. Process Res. Dev.*, 2015, **19**, 721–734.
6 K. Samanta, B. Chakravarti, J. K. Mishra, S. K. D. Dwivedi, L. V. Nayak, P. Choudhry, H. K. Bid, R. Konwar, N. Chattopadhyay and G. Panda, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 283–287.
7 P. Alfonsi, F. Adam, A. Passard, B. Guignard, D. I. Sessler and M. Chauvin, *Anesthesiology*, 2004, **100**, 37–43.
8 F. Narjes, B. Crescenzi, M. Ferrara, J. Habermann, S. Colarusso, M. R. R. Ferreira, I. Stansfield, A. C. Mackay, I. Conte, C. Ercolani, S. Zaramella, M.-C. Palumbi, P. Meuleman, G. Leroux-Roels, C. Giuliano, F. Fiore, S. D. Marco, P. Baiocco, U. Koch, G. Migliaccio, S. Altamura, R. Laufer, R. D. Francesco and M. Rowley, *J. Med. Chem.*, 2011, **54**, 289–301.
9 Selected examples: (*a*) S. S. Didwagh and P. B. Piste, *Int. J. ChemTech Res.*, 2013, **5**, 2199–2203; (*b*) H. Bienayme, L. Chene, S. Grisoni, A. Grondin, E. B. Kaloun, S. Poigny, H. Rahali and E. Tam, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 4830–4833; (*c*) E. Zhang, T. Xu, D. Wang, T. Huang, M. Yuan, J. Li and Y. Zou, *RSC Adv.*, 2014, **4**, 10022–10027; (*d*) W. Wu, Y. Zou, Y. Chen, J. Li, Z. Lv, W. Wei, T. Huang and X. Liu, *Green Chem.*, 2012, **14**, 363–370; (*e*) Y. Zou, E. S. Zhang, T. Xu, W. Wu, Y. Chen, M. Yuan, W. Wei and

X. J. Zhang, *RSC Adv.*, 2013, **3**, 6545–6550; (*f*) Y. Chen, Y. Zou, H. Y. Sun, X. Liu, C. F. Xiao, J. Sun, S. J. He and J. Li, *Synthesis*, 2011, 217–222; (*g*) W. Wei, E. S. Zhang, W. Wei, T. Huang, X. Liu, S. F. Yang and Y. Zou, *Chem. J. Chin. Univ.*, 2012, **33**, 2223–2228.

10 C.-S. Wang, R.-Y. Zhu, Y.-C. Zhang and F. Shi, *Chem. Commun.*, 2015, **51**, 11798–11801.

11 (*a*) Y.-L. Zhou, S.-W. Shen and F.-M. Liu, *J. Heterocycl. Chem.*, 2011, **48**, 105–112; (*b*) N. D. Adhikary and P. Chattopadhyay, *Eur. J. Org. Chem.*, 2011, 7346–7354; (*c*) P. Thansandote, E. Chong, K.-O. Feldmann and M. Lautens, *J. Org. Chem.*, 2010, **75**, 3495–3498.

12 D. B. Ramachary, V. V. Narayana, M. S. Prasad and K. Ramakumar, *Org. Biomol. Chem.*, 2009, **7**, 3372–3378.

13 (*a*) R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, 1963, **75**, 604–637; (*b*) R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, 1963, **2**, 633–645; (*c*) R. Huisgen, R. Grashey and J. Sauer, *The Chemistry of Alkenes*, ed. S. Patai, Interscience London, 1965.

14 (*a*) W. Zhang, Y. Lu, C. H.-T. Chen, D. P. Curran and S. Geib, *Eur. J. Org. Chem.*, 2006, 2055–2059; (*b*) S. Werner, S. D. Nielsen, P. Wipf, D. M. Turner, P. G. Chambers, S. J. Geib, D. P. Curran and W. Zhang, *J. Comb. Chem.*, 2009, **11**, 452–459; (*c*) Q. Lu, X. Huang, G. Song, C.-M. Sun, J. P. Jasinski, A. C. Keeley and W. Zhang, *ACS Comb. Sci.*, 2013, **15**, 350–355; (*d*) Y. Lu, S. J. Geib, K. Damodaran, B. Sui, Z. Zhang, D. P. Curran and W. Zhang, *Chem. Commun.*, 2010, **46**, 7578–7580; (*e*) W. Zhang, Y. Lu, C. H-T. Chen, L. Zeng and D. B. Kassel, *J. Comb. Chem.*, 2006, **8**, 687–695.

15 (*a*) W. Zhang, *Chem. Lett.*, 2013, **42**, 676–681; (*b*) W. Zhang, Y. Lu and S. Geib, *Org. Lett.*, 2005, **7**, 2269–2272; (*c*) Q. Lu, G. Song, J. P. Jasinski, A. C. Keeley and W. Zhang, *Green Chem.*, 2012, **14**, 3010–3012; (*d*) X. Zhang, S. Zhi, W. Wang, S. Liu, J. P. Jasinski and W. Zhang, *Green Chem.*, 2016, **18**, 2642–2646; (*e*) X. Zhang, K. Pham, S. Liu, M. Legris, A. Muthengi, J. P. Jasinski and W. Zhang, *Beilstein J. Org. Chem.*, 2016, **12**, 2204–2210; (*f*) X. Zhang, M. Legris, A. Muthengi and W. Zhang, *Chem. Heterocycl. Compd.*, 2017, **53**, 468–473; (*g*) X. Zhang, M. Liu, W. Qiu, J. Evans, M. Kaur, J. P. Jasinski and W. Zhang, *ACS Sustainable Chem. Eng.*, 2018, **6**, 5574–5579.

16 Selected monograph and reviews on (3+2) cycloadditions: (*a*) *Synthetic Application of 1,3-Dipolar Cycloaddition Chemistry toward Heterocycles and Natural Products*, ed. A. Padwa and W. H. Pearson, Wiley, Hoboken, 2003; (*b*) E. J. Kantorowski and M. J. Kurt, *Mol. Diversity*, 1996, **2**, 207–216; (*c*) C. Nájera and J. M. Sansano, *Curr. Org. Chem.*, 2003, **7**, 1105–1150; (*d*) I. Coldham and R. Hufton, *Chem. Rev.*, 2005, **105**, 2765–2809; (*e*) M. Bonin, A. Chauveau and L. Micouin, *Synlett*, 2006, 2349–2363.

17 Representative green metrics reviews: (*a*) F. Roschangar, R. A. Sheldon and C. H. Senanayake, *Green Chem.*, 2015, **17**, 752–768; (*b*) C. Jiménez-González, D. J. C. Constable and C. S. Ponder, *Chem. Soc. Rev.*, 2012, **41**, 1485–1498; (*c*) C. Jimenez-Gonzalez, C. S. Ponder, Q. B. Broxterman and J. B. Manley, *Org. Process Res. Dev.*, 2011, **15**, 912–917; (*d*) J. Augé, *Green Chem.*, 2008, **10**, 225–231; (*e*) J. Andraos, *Org. Process Res. Dev.*, 2005, **9**, 149–163; (*f*) D. J. C. Constable, A. D. Curzons and V. L. Cunningham, *Green Chem.*, 2002, **4**, 521–527; (*g*) C. Jiménez-González, A. D. Curzons, D. J. C. Constable, M. R. Overcash and V. L. Cunningham, *Clean Prod. Processes*, 2001, **3**, 35–41.

18 Recent examples: (*a*) R. A. Sheldon, *Green Chem.*, 2017, **19**, 18–43; (*b*) C. R. McElroy, A. Constantinou, L. C. Jones, L. Summerton and J. H. Clark, *Green Chem.*, 2015, **17**, 3111–3121; (*c*) T. V. T. Phan, C. Gallardo and J. Mane, *Green Chem.*, 2015, **17**, 2846–2852; (*d*) N. J. Willis, C. A. Fisher, C. M. Alder, A. Harsanyi, L. Shukla, J. P. Adams and G. Sandford, *Green Chem.*, 2016, **18**, 1313–1318; (*e*) S. Abou-Shehada, P. Mampuys, B. U. W. Maes, J. H. Clark and L. Summerton, *Green Chem.*, 2017, **19**, 249–258.

19 (*a*) R. A. Sheldon, *Green Chem.*, 2007, **9**, 1273–1283; (*b*) P. A. Wender, M. P. Croatt and B. Witulski, *Tetrahedron*, 2006, **62**, 7505–7511; (*c*) D. J. C. Constable, C. Jiménez-González and R. K. Henderson, *Org. Process Res. Dev.*, 2007, **11**, 133–137; (*d*) C. Jiménez-González, A. D. Curzons, D. J. C. Constable and V. L. Cunningham, *Clean Technol. Environ. Policy*, 2005, **7**, 42–50.