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Selective synthesis of three product classes from imine and carboxylic acid precursors via direct imine acylation

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**Three divergent Direct Imine Acylation (DIA) procedures are reported that allow the selective generation of δ-lactams, β-lactams and tetrahydropyrimidinones (via a novel three-component coupling) from imine and carboxylic acid precursors. All operate via initial *N*-acyliminium ion formation and diverge depending on the reaction conditions and nature of the substrates.**

Introduction

The selective synthesis of multiple products from common precursors represents an attractive way to streamline the synthesis of diverse molecules for biological evaluation.1 Compared with traditional linear synthetic methods, in which separate starting materials and routes are typically required to generate different target classes (Scheme 1A), there are clear benefits associated with divergent approaches (Scheme 1B). First, less time and money is spent preparing the requisite starting materials, and furthermore, in learning to control the outcome of the different reaction processes (whether that be by variation of reaction conditions, reagent quantities or the nature of any additional reagents/catalysts) insights into fundamental reactivity and mechanism are often gleaned.



**Scheme 1**. Linear and divergent synthesis

Recently, our groups2 and others3,4 have demonstrated the value of this type of approach in a range of unimolecular rearrangement reactions2 in which the reaction outcome is controlled by varying the catalyst; *e.g.* we have developed systems capable of delivering two,2a three2b and even six2c distinct products to generate aromatic, heterocyclic and spirocyclic scaffolds5 from simple precursors. Herein, we report our efforts to extend this idea to bimolecular processes, specifically the reactions of imines and carboxylic acids via Direct Imine Acylation (DIA).6 Significant effort has gone into the development of DIA in our laboratories in recent years, during which time we have demonstrated its utility for the synthesis of a large array of product classes, including heterocycles,6a-e spirocycles,6g β-lactams6f and natural products.6b,c,h A key feature of DIA is the *in situ* formation and subsequent cyclisation of reactive *N*-acyliminium ions,7 with representative examples shown in Scheme 2.6d Thus, stirring imine **1** and carboxylic acid **2a** with the coupling reagent T3P8 and NEt(*i*-Pr)2 in chloroform at room temperature results in the efficient formation of *N*-acyliminium ion **3a**, and following the addition of Lewis acid BF3·OEt2, this reactive intermediate undergoes cyclisation *in situ* to form δ-lactam **4a** in high overall yield.9 Conversely in a subsequent study,6f it was found that stirring the same reagent combination at 70 °C gave a different reaction outcome, with β-lactam **5a** being formed in 61% yield as a single diastereoisomer.10 The published syntheses of δ- and β-lactams **4a** and **5a** represent the only paired examples of this divergent reaction series performed to date, and therefore, in this research, it was decided to investigate whether similar divergent reactivity could be observed across a wider range of substrates. The results of these studies, along with the serendipitous discovery of a novel third reaction process, are described herein.



**Scheme 2**. Divergent DIA reactions.

## Results and Discussion

At the onset of this work, brief attempts were made to further optimise the published procedure for the synthesis of lactams **4a** and **5a** by varying the reaction stoichiometry and temperature of each process. Ultimately, none of the changes made resulted in an improvement in the yields of the target molecules,6d,f but these studies did lead to the serendipitous discovery of a new set of reaction conditions, capable of delivering a third distinct product framework. It was observed that upon increasing the amount of imine **1** used in the reaction, a more complex side product began to form, and that by using 3 equivalents of imine **1** and omitting NEt(*i*-Pr)2,this new product could be formed selectively in good yield at room temperature in chloroform (**6a**, 75% isolated yield following column chromatography, Scheme 3). Careful analysis using 1H and 13C NMR spectroscopy and mass spectrometry confirmed its identity as tetrahydropyrimidinone **6a**, which was isolated as mixture of 3 diastereoisomers (*dr* 6:2:1).11 The major diastereoisomer, which is believed to that shown in Scheme 3 based on NMR and n.O.e data, was isolated cleanly in 51% yield following column chromatography (for information on its stereochemical assignment, see later).



**Scheme 3**. Three-component synthesis of **6a**.

The product **6a** is composed of two imine units and one carboxylic acid, with a plausible mechanism for this three-component coupling given in Scheme 3. First, it is likely that *N-*acylation proceeds in the usual way to form *N*-acyliminium ion **3a**. It is known from our earlier work that a Lewis acidic additive is required to convert **3a** into δ-lactam **4a**,6d hence this pathway was negated, but the formation of β-lactam **5a** remained possible.6e However, in the presence of excess imine **1** this does not take place, and instead, it appears that the reactive *N*-acyliminium ion is trapped by this excess imine (**3a** + **1** → **7a**, presumably reversibly),6a to form an iminium adduct **7a**, which can then cyclise (via its enol/enolate form) to complete the synthesis of product **6a**. An alternative pathway (not shown) which cannot be ruled out, is that the same steps operate but imine dimerisation takes place before *N*-acylation, which would also lead to the formation of **7a** and its subsequent conversion into tetrahydropyrimidinone **6a**. Indeed, *N*-acylationfollowed by a hetero Diels–Alder reaction with another molecule of imine **1** (not shown) represents a third possibility,12 and it may be the case that two or more of these mechanisms operate simultaneously.

With three distinct products now accessible from coupling partners **1** and **2a**, attention turned to examining the scope of each process with respect to the carboxylic acid (Table 1).13,14 The yields quoted are isolated yields following column chromatography unless stated, and the highest yield for each distinct product is highlighted in bold type. Generally, tetrahydropyrimidinones **6a** and **6c**–**i** were formed as mixtures of diastereoisomers, which is not surprising given that three new stereogenic centers are formed in this reaction. In each case, the major diastereoisomer was partially or completely isolable; for full details, including *dr,* spectral data and synthetic procedures, see the Supporting Information, and for a discussion of the stereochemical assignments, see later.

While none of the new reaction series exhibited the same high levels of divergent reactivity observed for carboxylic acid **2a** (entries 1–3), several interesting trends emerged. For all three products to be formed in good yield across a reaction series, the electronics of the system must be very well-balanced. For example, while electron-rich benzoic acid derivative **2b** performed well under the conditions for δ-lactam formation (conditions **A**, entry 4, **4b**) and β-lactam formation (conditions **B**, entry 5, **5b**), the three-component coupling to form **6b** (conditions **C**, entry 6) failed, although these conditions did produce δ-lactam **4b** in higher yield than conditions **A**. The loss of chemoselectivity is likely to be because the aromatic ring is sufficiently electron-rich to react with the intermediate *N*-acyliminium ion without the need for a Lewis acidic additive.15 Unfortunately, aniline derivative **2c** was not compatible with conditions **A** (no identifiable products were isolated) but it was used to form β-lactam **5c** in reasonable yield.

Conversely, when the aromatic ring is electron-poor or electron-neutral (acids **2d–g**), the three-component coupling performs much better, but the δ-lactam formation fails, with anything less electron-rich than an anisole substituent not being nucleophilic enough to trap out the *N*-acyliminium ion to form δ-lactams **4c–g** (entries 10–21). More positively, β-lactam formation proceeded reasonably well for all of acids **2a–f**, with β-lactams **5a–f** being formed under the standard conditions in reasonable yields (47–69%), as single *trans-*diastereoisomers in each case. The only outlier in the β-lactam/benzoic acid series was acid **2g**, which did not form the expected β-lactams **5g** under conditions **B**, but instead formed tetrahydropyrimidinone **6g**.

**Table 1.** Divergent synthesis of δ-lactams, β-lactams and tetrahydropyrimidinones using DIA

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  |  | | | | |
| entry | Acid **2a–i** | Conditionsa | Isolated yield (%)b | | |
| **4a–g** | **5a–i** | **6a–i**c |
|  |  |  | **4a**, R2 = 3,4-OMe | **5a**, R1 = 3,4-MeO-C6H3 | **6a**, R1 = 3,4-MeO-C6H3 |
| 1 | **A** | **90** | 0 | 0 |
| 2 | **B** | 0 | **61** | 0 |
| 3 | **C** | 0 | 0 | **75** (*dr* 6:2:1) |
|  |  |  | **4b**, R2 = 3,4,5-OMe | **5b**, R1 = 3,4,5-MeO-C6H3 | **6b**, R1 = 3,4,5-MeO-C6H3 |
| 4 | **A** | 49 | 20% conversiond | 0 |
| 5 | **B** | 0 | **54** | 0 |
| 6 | **C** | **57** | 0 | 0 |
|  |  |  | **4c**, R2 = 4-NMe2 | **5c**, R1 = 4-Me2N-C6H3 | **6c**, R1 = 4-Me2N -C6H3 |
| 7 | **A** | 0 | 0 | 0 |
| 8 | **B** | 0 | **51** | 0 |
| 9 | **C** | 0 | 10% conversiond | **36** (*dr* 5:2) |
|  |  |  | **4d**, R2 = H | **5**d, R1 = Ph | **6d**, R1 = Ph |
| 10 | **A** | 0 | 24 | 0 |
| 11 | **B** | 0 | **47** | 5% conversiond |
| 12 | **C** | 0 | 0 | **69** (*dr* 10:6:3) |
|  |  |  | **4e**, R2 = 2-Br | **5e**, R1 = 2-Br-C6H4 | **6e**, R1 = 2-Br-C6H4 |
| 13 | **A** | 0 | 39 | 0 |
| 14 | **B** | 0 | **69** | 5% conversiond |
| 15 | **C** | 0 | 0 | **56** (single diastereomer) |
|  |  |  | **4f**, R2 = 4-F | **5**f, R1 = 4-F-C6H4 | **6f**, R1 = 4-F-C6H4 |
| 16 | **A** | 0 | 24 | 0 |
| 17 | **B** | 0 | **61** | 5% conversiond |
| 18 | **C** | 0 | 0 | **70** (*dr* 12:5:1) |
|  |  |  | **4g**, R2 = 4-NO2 | **5g**, R1 = 4-O2N-C6H4 | **6g**, R1 = 4- O2N -C6H4 |
| 19 | **A** | 0 | 0 | 48 |
| 20 | **B** | 0 | 0 | 50 |
| 21 | **C** | 0 | 0 | **60** (*dr* 3:1:1) |
|  |  |  |  | **5h**, R1 = CO2Et | **6h**, R1 = CO2Et |
| 22 | **B** | – | 0 | 30 |
| 23 | **C** | – | 0 | **87** (*dr* 11:5) |
|  |  |  |  | **5i**, R1 = CN | **6i**, R1 = CN |
| 24 | **C** | – | 0 | **69** (single diastereomer) |

a Conditions **A**: i) imine **1** (1 equiv.), acid **2** (1.2 equiv), T3P (1.5 equiv.), NEt(*i*-Pr)2 (1.85 equiv.), chloroform, RT, 40 min; ii) BF3·OEt2 (2 equiv.), RT, 1 h; Conditions **B**: imine **1** (1 equiv.), acid **2** (1.2 equiv), T3P (1.5 equiv.), NEt(*i*-Pr)2 (1.85 equiv.) chloroform, 70 °C, 20 h; Conditions **C**: imine **1** (3 equiv.), acid **2** (1 equiv), T3P (1.5 equiv.), chloroform, 70 °C, 20 h; b isolated yields following column chromatography. c Isolated as a mixture of diastereoisomers. For *dr* and isolated yields of the major isomers, see the Supporting Information. d Not isolated - conversion is based on integration of 1H NMR spectra of the unpurified reaction mixture

Another significant trend observed throughout this study is that the three-component couplings typically take place more readily for the most electron deficient substrates; *e.g.* acid **2g**,whichof the benzoic derivatives tested is the one with the most acidic methylene group, formed tetrahydropyrimidinone **6g** under all three sets of conditions (entries 19–21). Acids **2h** and **2i** (which have even more acidic methylene units) also only delivered tetrahydropyrimidinones **6h** and **6i**, which were formedin good yields, with no evidence of competing β-lactam formation (entries 22–24). More facile enol/enolate formation due to their acidic methylene groups likely accounts for this trend, as this might be expected to facilitate the final ring closing step (*i.e.* **7** → **6**).

As has already been alluded, the stereochemical outcomes of the tetrahydropyrimidinone-forming reactions are complicated. Mixtures of diastereoisomers were generally observed in the unpurified reaction mixtures, and the diastereomeric ratio changed following column chromatography, suggesting that epimerisation is taking place during isolation. Nonetheless, the major isomer was partially or completely isolable in each case. The basis of our stereochemical assignment is illustrated using tetrahydropyrimidinone **6d**, which was formed as a 10:6:3 mixture of diastereoisomers, from which clean portions of each isomer could be obtained for analysis. Thus, the relative stereochemistry of the three tetrahydropyrimidinone protons was assigned by the presence (for a *syn* relationship) or absence (for *anti*) of a nuclear Overhauser effect (n.O.e.) enhancement between these atoms, as indicated in Figure 1. Further support is gleaned from 3JH-H coupling constant data in their 1H NMR spectra (see the blue arrows, Figure 1), providing further support for the assigned *syn* (*J* = 4.9 Hz) or *anti* relationship (*J* = 10.8 Hz) between these two protons. Finally, the second most abundant isomer (**6d SECOND**) is a literature compound, and its NMR data fully agreed with those reported by Xu and co-workers.12 Interestingly, this diastereoisomer was the major isomer formed in the Xu study (in which a novel hetero-Diels–Alder approach was used), hence our DIA method is complementary, in that it affords a different diastereoisomer as the major product.



**Figure 1**. Three-component synthesis of **6a**.

By analogy, the major diastereoisomers for compounds **6a**, **6c**–**d** and **6f**–**g** are believed tobe the same as above (*c.f.* **6d MAJOR**with all three tetrahydropyrimidinone protons *syn*-disposed), based on them having very similar 3JH-H coupling constant for the coupled tetrahydropyrimidinone protons (*J* = 4.5–5.0 Hz). Conversely, the major diastereoisomers for tetrahydropyrimidinones **6e**, and **6h**–**I** are likely to correspond to either the ‘second’ or ‘minor’ isomer, as the equivalent 3JH-H coupling constants were in the 9.2–10.5 Hz range. More detailed studies would be needed to unambiguously establish the relative stereochemistry in each individual case; this is beyond the scope of this project, although we feel that the information accrued in this study, in tandem with that in the related paper by Xu,12 will help others to make reasonable stereochemical assignments for compounds of this class.

## Conclusions

In summary, three DIA procedures capable of delivering up to three distinct product scaffolds were examined across a series of nine imine/carboxylic acid pairings. Although variable selectivity was observed, 16 products were synthesised in total, with 14 of those being novel (full characterisation data and synthetic procedures can be found in the supporting information). Consistent reactivity trends were observed that will help to enable the reactivity of new examples to be better predicted: δ-lactam formation (procedure **A**) only works when electron-rich aromatics are used, β-lactam formation (procedure **B**) works well across a much wider range of substrates, failing only for the most electron-poor examples, while the novel three-component coupling (procedure **C**) was the most consistent method, producing the desired products **6** in all but one case. Given that tetrahydropyrimidinones are important targets in medicinal chemistry,16 it is out hope that this new method can be of value for the rapid construction of relatively complex analogues for biological evaluation, while it is also planned to investigate the possibility of using products of the form **6** to generate medium-sized ring scaffolds17 via reductive ring expansion procedures.18 Our efforts in both areas will be reported in due course.

### Conflicts of interest

There are no conflicts to declare.

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### Dedication

Dedicated to Professor Al Padwa to commemorate his many contributions to organic chemistry (and his 80th birthday)

## Notes and references

1. (a) F. Lovering, J. Bikker, C. Humblet, *J. Med. Chem*. 2009, **52**, 6752; (b) M. Aldeghi, S. Malhotra, D. L. Selwood, A. W. E. Chan, *Chem. Biol. Drug Des*. 2014, **83**, 450; (c) A. Karawajczyk, F. Giordanetto, J. Benningshof, D. Hamza, T. Kalliokoski, K. Pouwer, R. Morgentin, A. Nelson, G. Muller, A. Pierchot, D. Tzalis, *Drug Discov. Today* 2015, **20**, 1310.
2. (a) M. J. James, R. E. Clubley, K. Y. Palate, T. J. Procter, A. C. Wyton, P. O’Brien, R. J. K. Taylor, W. P. Unsworth, *Org. Lett.* 2015, **17**, 4372; (b) J. T. R. Liddon, M. J. James, A. K. Clarke, P. O’Brien, R. J. K. Taylor, W. P. Unsworth, *Chem. Eur. J.* 2016, **22**, 8777; (c) M. J. James, P. O’Brien, R. J. K. Taylor, W. P. Unsworth, *Angew. Chem. Int. Ed.* 2016, **55**, 9671.
3. For a review on catalyst selective synthesis, see: Mahatthananchai, J.; Dumas, A. M.; Bode, J. W. *Angew. Chem. Int. Ed*. **2012**, *51*, 10954.
4. For more recent examples, see: (a) J. D. Dooley, S. Reddy Chidipudi, H. W. Lam, *J. Am. Chem. Soc*. 2013, **135**, 10829; (b) D. S. B. Daniels, A. S. Jones, A. L. Thompson, R. S. Paton, E. A. Anderson, *Angew. Chem. Int. Ed*. 2014, **53,** 1915; (c) L. Xu, H. Li, Z. Liao, K. Lou, H. Xie, H. Li, W. Wang, *Org. Lett*. 2015, **17**, 3434; (d) J.-Y. Liao, P.-L. Shao, Y. Zhao, *J. Am. Chem. Soc*. 2015, **137**, 628; (e) A. Galván, J. Calleja, A. B. González-Pérez, R. Álvarez, A. R. de Lera, F. J. Fañanás, F. Rodríguez, *Chem. Eur. J*. 2015, **21**, 16769; (f) D. Y. Li, H. J. Chen, P. N. Liu, *Angew. Chem. Int. Ed*. 2016, **55**, 373; (g) Q.-Q. Cheng, J. Yedoyan, H. Arman, M. P. Doyle, *J. Am. Chem. Soc*. 2016, **138**, 44.
5. For related work on spirocycle synthesis, see: (a) W. P. Unsworth, J. D. Cuthbertson, R. J. K. Taylor, *Org. Lett.* 2013, **15**, 3306; (b) M. J. James, J. D. Cuthbertson, P. O’Brien, R. J. K. Taylor, W. P. Unsworth, *Angew. Chem. Int. Ed.* 2015, **54**, 7640; (c) A. K. Clarke, M. J. James, P. O’Brien, R. J. K. Taylor, W. P. Unsworth, *Angew. Chem. Int. Ed.* 2016, **55**, 13798; (d) J. T. R. Liddon, A. K. Clarke, R. J. K. Taylor, W. P. Unsworth, *Org. Lett.* 2016*,* **18***,* 6328.
6. (a) W. P. Unsworth, C. Kitsiou C.; R. J. K. Taylor, *Org. Lett*. 2013, **15**, 258; (b) W. P. Unsworth, K. A. Gallagher, M. Jean, J. P. Schmidt, L. J. Diorazio, R. J. K. Taylor, *Org. Lett*. 2013, **15**, 262; (c) W. P. Unsworth, R. J. K. Taylor, *Org. Biomol. Chem*. 2013, **11**, 7241; (d) W. P. Unsworth, G. Coulthard, C. Kitsiou, R. J. K. Taylor, *J. Org. Chem*. 2014, **79**, 1368; (e) C. Kitsiou, W. P. Unsworth, G. Coulthard, R. J. K. Taylor, *Tetrahedron* 2014, **70**, 7172; (f) G. Coulthard, W. P. Unsworth, R. J. K. Taylor, *Tetrahedron Lett.* 2015, **56**, 3113; (g) S. J. Chambers, G. Coulthard, W. P. Unsworth, P. O’Brien, R. J. K. Taylor, *Chem*. *Eur. J.* 2016, **22**, 6496; (h) T. O. Ronson, C. Kitsiou, W. P. Unsworth, R. J. K. Taylor, *Tetrahedron* 2016, **72**, 6099; (i) W. P. Unsworth, R. J. K. Taylor, *Synlett* 2016, 2051.
7. For cyclisation reactions involving *N*-acyliminium ions, see: (a) W. N. Speckamp, H. Hiemstra, *Tetrahedron* 1985, **41**, 1985, 4367; (b) W. N. Speckamp, M. J. Moolenaar, *Tetrahedron* 2000, **56**, 3817; (c) B. E. Maryanoff, H.-C. Zhang, J. H. Cohen, I. J. Turchi, C. A. Maryanoff, *Chem. Rev*. 2004, **104**, 1431; (d) A. Yazici, S. G. Pyne, *Synthesis* 2009, 339; (e) A. Yazici, S. G. Pyne, *Synthesis* 2009, 513; (f) S. T. Le Quement, R. Petersen, M. Meldal, T. E. Nielsen, T. E. *Biopolymers* (Peptide Science), 2010, **94**, 242.
8. H. Wissmann, H.-J. Kleiner, *Angew. Chem. Int. Ed*. 1980, 19, 133.
9. For related processes involving the coupling of imines with *in situ* activated carboxylic acids, see: (a) M. W. Smith, R. Hunter, D. J. Patten, W. Hinz, *Tetrahedron Lett.* 2009, **50**, 6342; (b) F. Pin, S. Comesse, A. Daϊch, *Tetrahedron* 2011, **67**, 5564; (c) Y. Yang, C. Zhu, M. Zhang, S. Huang, J. Lin, X. Pan, W. Su, *Chem. Commun.* 2016, **52**, 12869.
10. For related β-lactam syntheses and mechanistic studies, see: (a) F. P. Cossío, A. Arrieta, M. A. Sierra, *Acc. Chem. Res.* 2008, **41**, 925; (b) K. S. Crichfield, J. E. Hart, J. T. Lampert, R. K. Vaid, *Synth. Commun*. 2000, **30**, 3737; (c) M. Zarei, *Monatsh. Chem.* 2014, **145**, 1495; (d) L. Jiao, Y. Liang, J. Xu, *J. Am. Chem. Soc*. 2006, **128**, 6060; (e) Y. Liang, L. Jiao, S. W. Zhang, Z. X. Yu, J. X. Xu, *J. Am. Chem. Soc*. 2009, **131**, 1542.
11. Synthetic procedure and spectral data for **6a**: To a solution of carboxylic acid **2a** (100 mg, 0.510 mmol) in CHCl3 (7 mL) was added T3P (487 mg, 0.765 mmol, 1.5 equiv., 50% wt. solution in THF) followed by imine **1** (202 mg, 1.530 mmol, 3 equiv.). The resulting solution was stirred at 70 °C for 20 h, before being quenched by the addition of saturated aqueous NH4Cl (10 mL). The aqueous layer was extracted with DCM (3 x 10 mL), dried (MgSO4) and concentrated under reduced pressure (the *dr* was 10:3:2:2 at this stage). The product was then purified by column chromatography (6:4 ethyl acetate:hexane), affording the title compound **6a** (169 mg, 75% overall) as a mixture of three diastereoisomers in a ratio of roughly 12:4:2. From this mixture, the major isomer was isolated cleanly as an orange oil (114 mg, 51%), with spectral data for the major isomer provided: νmax (thin film)/cm−1 2931, 1639, 1514, 1462, 1262, 1237, 1028, 909, 728; δH (400 MHz, CDCl3) 7.53–7.49 (1 H, m, Ar-H), 7.36–7.20 (4 H, m, Ar-H), 7.14 (1 H, t, *J* 7.0, Ar-H), 7.09 (1 H, t, *J* 7.0, Ar-H), 7.02 (1 H, d, *J* 7.5, Ar-H), 6.68–6.61 (2 H, m, Ar-H), 6.51 (1 H, d, *J* 8.0, Ar-H), 5.27 (1 H, s), 4.70 (1 H, d, *J* 4.5), 4.22 (1 H, d, *J* 4.5), 3.90 (1 H, ddd, *J* 13.0, 10.5, 6.0), 3.71 (3 H, s), 3.74–3.66 (1 H, m), 3.49 (3 H, s), 3.39 (1 H, dt, *J* 11.5, 4.5), 3.15–2.93 (3 H, m), 2.72 (1 H, app. dt, *J* 16.0, 4.0), 2.59 (1 H, ddd, *J* 11.5, 10.0, 4.0); 13C NMR (101 MHz, CDCl3) δ = 169.7, 147.7, 147.5, 137.4, 135.9, 135.3, 134.5, 129.5, 129.1, 128.2, 127.9, 126.9, 126.7, 126.6, 125.8, 124.5, 123.1, 113.6, 110.3, 74.2, 60.9, 55.7, 55.6, 52.1, 46.5, 41.7, 29.0, 27.6 HRMS (ESI+): Found: 441.2141; C28H29N2O3+ (MH+) Requires 441.2173 (4.0 ppm error).
12. For a hetero-Diels–Alder procedure leading to the formation of tetrahydropyrimidinones, see: (a) Z. Yang, W. He, B. Cheng, J. Xu, *J. Org. Chem.* 2016, **81**, 4506. For a related study on sulfonyl derivatives, see: (b) Q. Wu, Z. Yang, J. Xu, *Org. Biomol. Chem.* 2016, **14**, 7258.
13. To allow for easier comparison, chloroform was used as the solvent across all three reaction series, but note that in our earlier work (see reference 6), DCM, THF and toluene have all been shown to be compatible solvents in DIA reactions. AlCl3 and TFA have also been used as alternative acidic additives.
14. A range of imines other than **1** have been used as starting materials in DIA reactions to make products of the form **4** and **5** (see reference 6). Other cyclic imines also appear to be compatible with procedure C, including substituted dihydroisoquinoline derivatives and non-aromatic variants; these results will be described in due course.
15. In our previous work, we have shown that electron rich indoles can trap *N*-acyliminium ions without Lewis acid activation in a related process, see reference 6g.
16. See references 6a, 6d, 12 and references cited therein.
17. For the medicinal importance of medium sized ring compounds, see: (a) R. A. Bauer, T. A. Wenderski, D. S. Tan, *Nat. Chem. Bio*. 2013, **9**, 21; (b) A. Hussain, S. K. Yousuf, D. Mukherjeem, *RSC Adv*. 2014, **4**, 43241; (c) C. Kitsiou, J. J. Hindes, P. I’Anson, P. Jackson, T. C. Wilson, E. K. Daly, H. R. Felstead, P. Hearnshaw, W. P. Unsworth, *Angew. Chem. Int. Ed*. 2015, **54**, 15794; (d) L. G. Baud, M. A. Manning, H. L. Arkless, T. C. Stephens, W. P. Unsworth, *Chem. Eur. J*. 2017, **9**, 2225; (e) T. C. Stephens, M. Lodi, A. M. Steer, Y. Lin, M. T. Gill, W. P. Unsworth, W. P. *Chem. Eur. J*. doi: 10.1002/chem.201703316.
18. For reductive ring expansion reactions, see: (a) H. M. Wasserman, R. P.; Robinson, H. Matsuyama, *Tetrahedron Lett.* 1980, **21**, 3493; (b) M. J. Calverley, J. Harley-Mason, *Tetrahedron Lett.* 1981, **22**, 1631; (c) J. Bonjoch, J.-C. Fernàndez, N. Valls, *J. Org. Chem.* 1998, **63**, 7338; (d) M. Traoré, F. Mietton, D. Maubon, M. Peuchmaur, F. F. Hilário, R. Pereira de Freitas, A. Bougdour, A. Curt, M. Maynadier, H. Vial, H. Pelloux, M.-A. Hakimi, Y.-S. Wong, *J. Org. Chem.* 2013, **78**, 3655; (e) J. R. Donald, W. P. Unsworth, *Chem. Eur. J*. 2017, **23**, 8780.