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Direct Imine Acylation: Rapid Access to Diverse Heterocyclic Scaffolds

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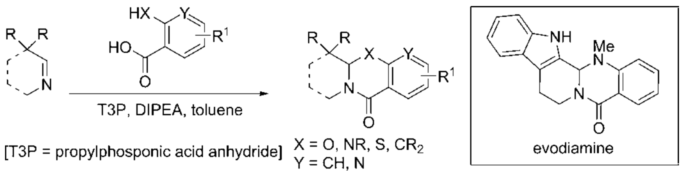
ABSTRACT

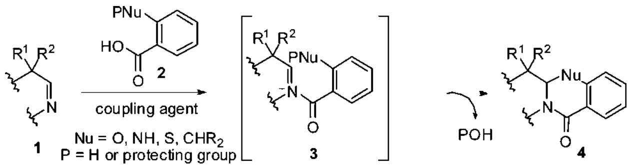


A simple and efficient procedure to prepare a range of diverse heterocycles by the direct acylation of imines using a variety of functionalized benzoic acids is described. The methodology features a novel method for *N*-acyliminium ion generation followed by in situ intramolecular trapping by oxygen-, nitrogen-, sulfur- and carbon-based nucleophiles. Preliminary mechanistic studies, using ReactIR, are also reported.

New methods for the synthesis of polycyclic heterocycles are invaluable in the pharmaceutical and agrochemical industries.[1] The potential of such methodology is at its greatest when it facilitates the synthesis of a diverse range of substrate classes, is high yielding and operationally simple, and results in a rapid increase in molecular complexity from simple readily available starting materials.[2,3]

We report a novel scaffold diversity approach built around the concept of direct imine acylation (DIA) as illustrated in Scheme 1. It was planned that acylation of an imine (**1**) with a suitably functionalized carboxylic acid (**2**) would generate an *N*-acyliminium ion (**3**) in anticipation that a nucleophile or pronucleophile built into the acid coupling partner would initiate in situ cyclization. We now report the successful implementation of the DIA approach using functionalized benzoic acids to generate a range of diverse heterocycles (**4**).

Scheme 1. Direct Imine Acylation



The use of *N*-acyliminium ions in heterocycle synthesis is well documented,[4] but in the vast majority of examples, the *N*-acyliminium species are generated from preformed systems, usually by a regioselective partial imide reduction or a regioselective amide oxidation.[4] The key advantage to our convergent approach is the direct use of a carboxylic acid (rather than activated derivatives)[5,6] in *N*-acyliminium generation allowing a range of *ortho*-functional groups to be tolerated. The ready availability of starting materials and the convergent nature of the process gives DIA great potential, particularly with regards to diversity-oriented synthesis.[2]

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(1) (a) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893. (b) *Comprehensive Heterocyclic Chemistry III*; Katritzky, A. R., Ramsden, C. A., Scriven, E. F. V., Taylor, R. J. K., Eds.; Elsevier: Oxford, 2008 and references therein.

(2) (a) Morton, D.; Leach, S.; Cordier, C.; Warriner, S.; Nelson, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 104. (b) Spandl, R. J.; Bender, A.; Spring, D. R. *Org. Biomol. Chem.* **2008**, *6*, 1149. (c) Lipkus., A. R.; Yuan, Q.; Lucas, K. A.; Funk, S. A.; Bartelt, W. F., III; Schenck, R. J; Trippe, A. J. *J. Org. Chem.* **2008**, *73*, 4443.

(3) (a) Taylor, R. J. K.; Reid, M.; Foot, J. S.; Raw, S. A. *Acc. Chem. Res.* **2005**, *38*, 851. (b) Raw, S. A.; Taylor, R. J. K. *J. Am. Chem. Soc.* **2004**, *126*, 12260. (c) Klein, J. E. M. N.; Perry, A.; Pugh., D. S.; Taylor, R. J. K. *Org. Lett.* **2010**, *12*, 3446 and references therein.

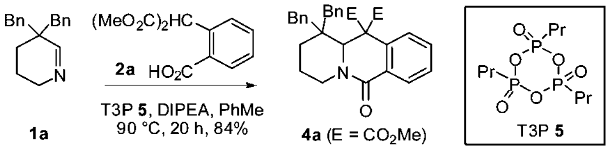
(4) (a) Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 1985. 4367. (b) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817. (c) Maryanoff, B. E.; Zhang, H.-C.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem. Rev.* **2004**, *104*, 1431.

(5) For early examples using acid chlorides, acyl fluorides, anhydrides, etc., see (a) Ziegler, E.; Hanus, H. D. *Monatsh. Chem.* **1965**, *96*, 411. (b) Ziegler, E.; Kollenz, G.; Kappe, T. *Monatsh. Chem.* **1968**, *99*, 804. (c) Kametani, T.; Higa, T.; Van Loc, C.; Ihara, M.; Koizumi, M.; Fukumoto, K. *J. Am. Chem. Soc.* **1976**, *98*, 6186. (d) Castagnioli, N., Jr. *J. Org. Chem.* **1969**, *34*, 3187.

10.1021/ol303073b

The viability of the DIA concept was established using the novel cyclic imine **1a** and the benzoic acid **2a** (Scheme 2). Propylphosphonic acid anhydride (T3P, **5**)[7] in toluene was chosen to effect the direct coupling, as it is nontoxic and the byproducts are easily removed by aqueous extraction.[8]

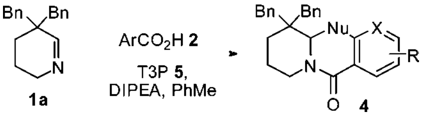
Scheme 2. Reaction of Imine **1a** with Acid **2a**

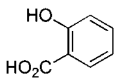
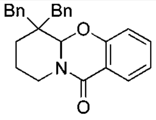
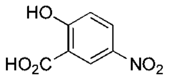
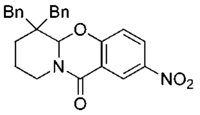
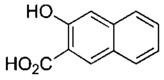
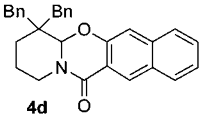
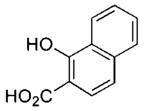
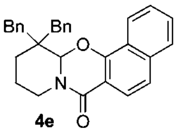
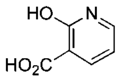
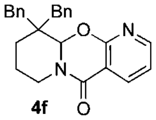
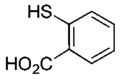
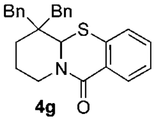
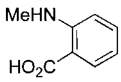
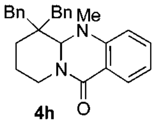
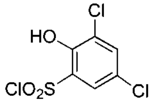
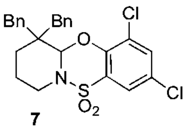


We were delighted to observe the efficient formation of tricyclic lactam **4a** in 84% yield after chromatography. Additional experiments in which the same coupling was attempted in the absence of either DIPEA or T3P led only to the recovery of the starting materials, with no evidence of the cyclized product **4a**.

We then went on to explore DIA using a range of substituted benzoic acid derivatives (**2b**–**2h**, Table 1). As can be seen, salicylic acid derivatives are extremely well tolerated, affording products in excellent yields (Table 1, entries i–vi).[9] The DIA methodology is not restricted to the trapping of the intermediate *N*-acyliminium salt with carbon and oxygen nucleophiles. For example, under the standard T3P conditions, treatment of imine **1a** with thiosalicylic acid **2g** gave thiazinone **4g** (entry vii), and *N*-methyl anthranilic acid **2h** underwent cyclization to the diazine **4h** (entry viii), both in near quantitative yields. The final example in Table 1 (entry ix) illustrates that the DIA concept need not be limited to acylation, as demonstrated by the formation of sulfonamide-containing dioxo(dihydro)-benzoxathiazine **7** from reaction of imine **1a** with commercially available sulfonyl chloride **6**.

Table 1. Acid Scope in Direct Imine Acylation/Cyclization[a]



entry	acylating agent	product	yield[b]
i	 **2b**	 **4b**	83%[c],[d]
ii iii	 **2c**	 **4c**	91% 90%[e]
iv	 **2d**	 **4d**	95%
v	 **2e**	 **4e**	92%
vi	 **2f**	 **4f**	97%
vii	 **2g**	 **4g**	96%[f]
viii	 **2h**	 **4h**	97%[c]
ix	 **6**	 **7**	92%[g]

[a] Unless stated, reactions were performed on a 0.1–0.3 mmol scale using T3P, DIPEA in PhMe at 90 °C for 20 h. [b] Isolated yields after purification by column chromatography. [c] Reaction performed in the absence of T3P gave 0% yield of product. [d] Reaction performed in the absence of DIPEA gave 0% yield of product. [e] Reaction performed on a 3 mmol scale under the standard conditions. [f] Reaction performed in the absence of T3P gave 20% yield of product. [g] Compound **6** was stirred with imine **1a** and DIPEA in PhMe at 90 °C for 20 h.

We next went on to confirm that the scope of this methodology is equally versatile in terms of the imine substrate (Table 2). First, 3,4-dihydroisoquinoline (**1b**) gave adducts **4i** and **4j** in reasonable and excellent yields, respectively (entries i and ii); this substructure features heavily in natural products and in pharmaceutically important compounds,[10] and applications of this DIA sequence in target synthesis are anticipated. Further diversity can be achieved by varying the ring size of the imine, as demonstrated by the DIA reaction of the disubstituted 1-pyrroline **1c** affording adduct **4k** in excellent yield (entry iii).

Synthetic applications of acyclic *N*-acyliminium salts are limited as they are much less stable than their cyclic analogues, particularly with respect to hydrolysis.[4,11]

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(6) For more recent examples using acid chlorides, acyl fluorides, anhydrides, etc., see (a) Strumberg, D.; Pommier, Y.; Paull, K.; Jayaraman, M.; Nagafuji, P.; Cushman, M. *J. Med. Chem.* **1999**, *42*, 446. (b) Sieck, O.; Ehwald, M.; Liebscher, J. *Eur. J. Org. Chem.* **2005**, *4*, 663. (c) Chen, Z.; Hu, G.; Chen, J.; Li, D.; Chen, J.; Li, Y.; Zhou, H.; Xie, Y. *Bioorg. Med. Chem.* **2009**, *17*, 2351. (d) Johannes, K.; Martens, J. *Tetrahedron* **2010**, *66*, 242 and references therein.

(7) Wissmann, H.; Kleiner, H.-J. *Angew. Chem., Int. Ed.* **1980**, *19*, 133.

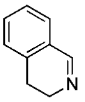
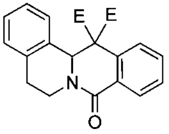
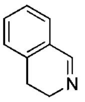
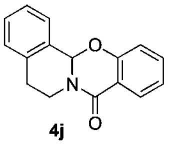
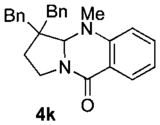
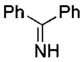
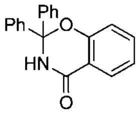
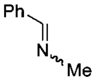
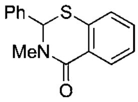
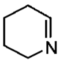
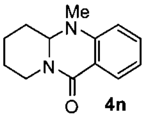
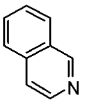
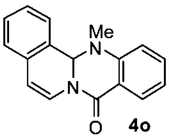
(8) Successful coupling was also achieved using T3P, HATU or DCC, each with DIPEA, in refluxing $CHCl_3$ or toluene at 90 °C.

(9) After the completion of this work, a single example of *N*-acyliminium ion formation by direct carboxylic acid coupling to imines was reported using DCC/DMAP to couple a substituted benzoic acid to dihydrocarboline: Pin, F.; Comesse, S.; Daïch, A. *Tetrahedron* **2011**, *67*, 5564.

(10) Chrzanowska, M.; Rozwadowska, M. D. *Chem. Rev.* **2004**, *104*, 3341 and references therein.

(11) Böhme, H.; Hartke, K. *Chem. Ber.* **1963**, *96*, 600.

Table 2. Imine Scope in Direct Imine Acylation/Cyclization[a]

entry	imine	acid	product	yield[b]
i	 **1b**	**2a**	 **4i** (E = CO_2Me)	69%
ii	 **1b**	**2b**	 **4j**	89%
iii[c]	 **1c**	**2h**	 **4k**	87%
iv	 **1d**	**2b**	 **4l**	60%
v	 **1e**	**2g**	 **4m**	99%
vi	 **1f**	**2h**	 **4n**	40%
vii	 **1g**	**2h**	 **4o**	94%

[a] Reactions were performed on a 0.1−0.3 mmol scale using T3P, DIPEA in PhMe at 90 °C for 20 h. [b] Isolated yields after purification by column chromatography. [c] Imine **1f** was generated by deoligomerization of dodecahydro-4a,8a,12a-triazatriphenylene in situ.

DIA technology overcomes this problem by forming and trapping the unstable *N*-acyliminium ions in situ, and so acylic imines **1d** and **1e** undergo DIA reactions giving adducts **4l** and **4m** (entries iv and v). Dodecahydro-4a,8a,12a-triazatriphenylene, the trimeric form of imine **1f**,[12] was employed directly in a DIA procedure with anthranilic acid **2h** to produce diazine **4n** (entry vi), demonstrating that even unstable imines, which are prone to oligomerization and enamine formation, can be compatible with the DIA protocol. Finally (entry vii), we demonstrated that isoquinoline (**1g**) could be successfully employed in a DIA coupling with anthranilic acid **2h**, overcoming loss of aromaticity,[13] to afford the tetracyclic nitrogen heterocycle **4o** in 94% yield. This example indicates that DIA will not be limited to simple imines. It should also be noted that, for comparison purposes, all reactions were carried out using the standard conditions and that optimization should lead to an increase in yield in the majority of cases.

Two extreme mechanistic pathways could be envisaged for these processes: (i) *N*-acylation takes place first and is followed by an intramolecular cyclization (as we have assumed, Scheme 1), or (ii) nucleophilic addition of the *ortho*-substituent onto the imine occurs first, followed by intramolecular acylation. An added complication is that imino-ketene intermediates have been proposed for the acylation step in related anthranilic acid processes.[5c,6d] Of course, it is not unreasonable that the exact mechanism is substrate-dependent, or that more than one mechanism may operate in competition. However, the fact that no reaction occurs with most examples in the absence of the T3P coupling agent provides corroboration for the theory that the initial step involves *N*-acylation of the imine.[14] To shed more light on the process, an in situ ReactIR study was carried out to study the DIA reaction of imine **1a** with 5-nitro-salicylic acid **2c**.[15] A more detailed analysis is included in the Supporting Information, but this ReactIR study rules out a ketene intermediate and is consistent with a process involving (i) rapid carboxylic acid activation, (ii) imine *N*-acylation generating a short-lived *N*-acyliminium ion **3c** (Peak 1, Figures 1 and 2), (iii) reversible trapping of the iminium intermediate by excess DIPEA in the reaction mixture, affording an ammonium salt **8** (Peak 2, Figures 1 and 2), and (iv) regeneration of the *N*-acyliminium intermediate **3c** and cyclization to give the product **4c** (Peak 3, Figures 1 and 2).

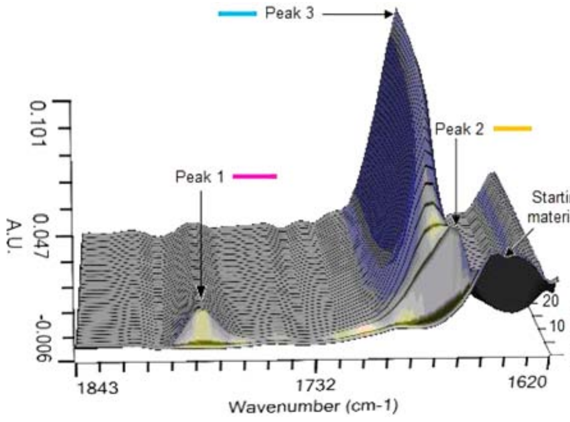


Figure 1. 3D ReactIR plot of atomic absorption against wavenumber and time.

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(12) (a) Schöpf, C.; Komzak, A.; Braun, F.; Jacobi, E.; Bormuth, M.-L.; Bullnheimer, M.; Hagel, I. *Liebigs Ann.* **1948**, *559*, 1. (b) Barker, G.; McGrath, J. L.; Klapars, A.; Stead, D.; Zhou, G.; Campos, K. R.; O'Brien, P. *J. Org. Chem.* **2011**, *76*, 5936.

(13) Sieck, O.; Ehwald, M.; Liebscher, J. *Tetrahedron Lett.* **2000**, *29*, 5479.

(14) With thiosalicylic acid **2g** (Table 1, entry vi) a small amount (20%) of coupled product **4g** was observed in the absence of T3P, and so some intermolecular imine addition may be taking place in this system.

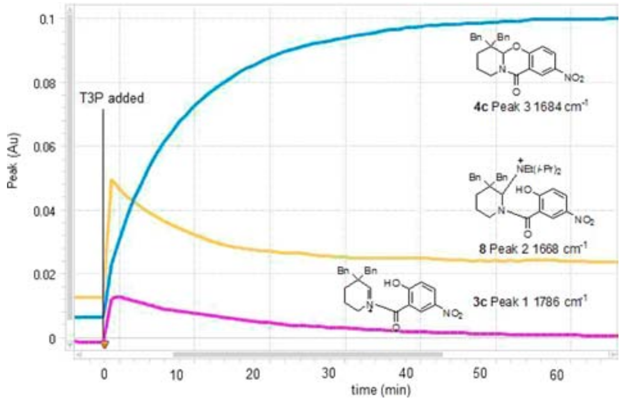
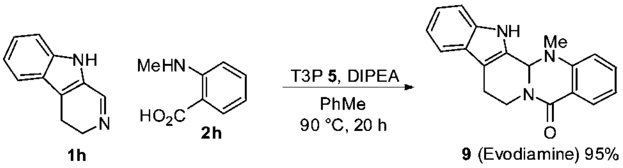


Figure 2. 2D ReactIR plot of atomic absorption units of the wavenumbers 1786, 1668 and 1684 cm^{-1} against time.

Finally, the value of DIA has been illustrated by the rapid and efficient synthesis of evodiamine (**9**), a natural product isolated from *Evodiae fructus*.[16] Evodiamine has been shown to reduce fat uptake in animal studies[16b] and has been included in some dietary preparations, particularly in the Chinese herbal weight loss supplement, Wu-Chu-Yu. More recently, it has been demonstrated that evodiamine is a novel inhibitor of human DNA topoisomerase I.[16c] Starting from dihydrocarboline **1h**,[17] treatment with *N*-methyl anthranilic acid **2h** and T3P under standard DIA conditions produced evodiamine (**9**) in a one-pot process in 95% yield as a crystalline product (Scheme 3).

In summary, DIA methodology has been shown to be a reliable and versatile tool for the synthesis of a range of polycyclic heterocyclic scaffolds. The procedure uses readily available nontoxic reagents, is operationally simple and is relatively insensitive to both water and air. Crucially, the in situ generation and trapping of the transient *N*-acyliminium ion avoids the need to isolate unstable *N*-acyliminium ion precursors. The mild nature of the reagents used for the *N*-acylation is important in this regard, as they have been shown to be compatible with unprotected nucleophiles, which may not survive the typically much harsher conditions used in most of the existing procedures for *N*-acyliminium ion generation. The potential substrate scope is very large, and in most cases the isolated yields were found to be very high under identical conditions, suggesting that diverse targeted libraries of compounds should be readily synthesized using DIA, requiring little or no optimization. It is also worth noting that while for the purpose of the publication, column chromatography was used to ensure analytically pure products were obtained, in the majority of cases no discernible byproducts from the reagents, or reaction side-products, were observable in the ^{1}H NMR spectra of the unpurified products. We are confident that in time the reactions described will be further optimized and augmented with new variants, as well as finding use in target synthesis.[18]

Scheme 3. Application of DIA to Prepare Evodiamine



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Supporting Information Available. Synthetic procedures, ReactIR details and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Acid **2c** was chosen, as this substrate was found to be particularly reactive; a lower temperature was needed to be compatible with the ReactIR probe, and this reaction proceeded efficiently in 1 h at 50 °C.

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The authors declare no competing financial interest.