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Substrate scope in the direct imine acylation of *ortho*-substituted benzoic acid derivatives: the total synthesis (±)-cavidine

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Dedicated to the memory of Sandy McKillop—colleague, mentor, collaborator and friend

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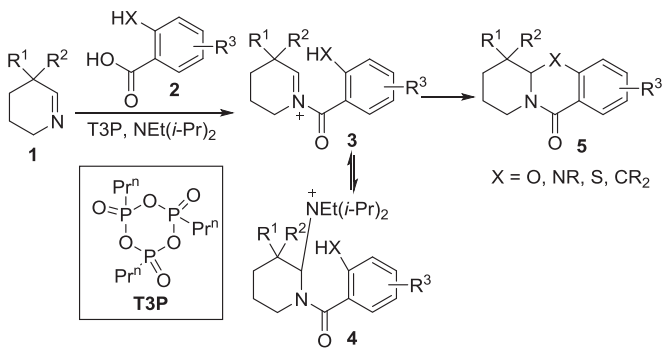
ABSTRACT

The direct imine acylation (DIA) and subsequent cyclisation of a range of imines with *ortho*-substituted benzoic acid derivatives is described. Variation in the coupling reagents, imine and benzoic acid were all examined. The DIA procedure was also applied in the total synthesis of (±)-cavidine.

1. Introduction

The controlled synthesis of diverse heterocycles is crucial in both the pharmaceutical and agrochemical industries.[1] Novel methods that expedite their synthesis are therefore of great importance, especially those which furnish a range of diverse scaffolds whose biological activity has not previously been well-examined. Such diversity-oriented-synthesis[2] has attracted widespread interest in recent years as a strategy to accelerate the discovery of new therapeutically important compounds.

In order for these methods to be widely adopted by the synthetic community, both in industry and in academia, various conditions must be satisfied: the new methods must be reliable, operationally simple, high yielding and crucially be capable of generating a broad range of structures without significant optimisation. Our research group recently reported one such method, based on the concept of 'Direct Imine Acylation' (DIA).[3] This methodology centres on a novel way to generate *N*-acyliminium ions and their subsequent reaction with tethered nucleophiles. The initial communication focused on the direct coupling of a range of imines (**1**) with *ortho*-substituted benzoic acids (**2**) using propylphosphonic acid anhydride (T3P)[4] and NEt(*i*-Pr)$_2$ (DIPEA) to activate the benzoic acid towards nucleophilic attack by the imine nitrogen to form the key *N*-acyliminium ion **3** (Scheme 1). An accompanying mechanistic study, in which the progress of the reaction was monitored in situ by IR spectroscopy using ReactIR™, shed further light on the process. It is proposed that the *N*-acyliminium ion **3** exists only briefly and is trapped by excess DIPEA in the reaction mixture, affording ammonium salt **4**. This process is reversible and so the extrusion of DIPEA results in the regeneration of the *N*-acyliminium ion **3**, which is subsequently trapped by the *ortho*-nucleophile in a one-pot process, driving the equilibrium towards the formation of the desired heterocyclic product **5**.



Scheme 1. Direct imine acylation.

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Diversity was initially examined both in terms of the imine **1** and the benzoic acid derivative **2**. Most notably, the methodology was shown to be compatible with phenols, anilines, thiols and carbon pro-nucleophiles as the *ortho*-substituent on the benzoic acid (**2**, X=O, NMe, S, $C(CO_2Me)_2$). Furthermore, we more recently disclosed preliminary results, which demonstrate that DIA is also compatible with aliphatic carboxylic acids.[5] Protected aliphatic alcohols, protected amines, thiols and a range of carbon pro-nucleophiles can also be tethered to the carboxylic acid and react with the *N*-acyliminium ion using broadly similar conditions to those described above, dramatically increasing the range of heterocyclic scaffolds accessible. DIA has also been used in target synthesis; the total synthesis of evodiamine **6**[3,6] was completed in high yield (95%, see later) and DIA methodology was also used to construct the spirooxoquinolizidinone ring system of the proposed structures of the complex marine natural product 'upenamide **7** (Fig. 1).[7]

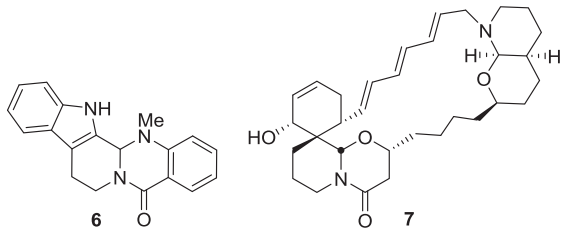


Fig. 1. The structure of evodiamine **6** and one of the proposed structures of 'upenamide **7**.

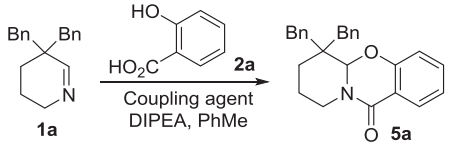
Herein we report extended substrate scoping studies for DIA using benzoic acid derivatives. We also describe the application of DIA in the total synthesis of the natural product (±)-cavidine.

2. Results and discussion

In our initial communication, all of the DIA reactions reported were performed by simply mixing the imine, carboxylic acid, T3P and DIPEA in toluene and heating to 90 °C in most cases, or 120 °C if t.l.c. analysis indicated that the reaction was incomplete after 20 h. All of the reagents were used as supplied, without drying or purification, and it was not necessary to exclude air from the reaction. We have since discovered that both CDI and DCC may be used in place of T3P in the reaction of imine **1a** with salicylic acid **2a** (Table 1, entries 1–3). The same reaction was also tested using EDC as the coupling reagent but this failed, most likely because of the poor solubility of EDC in toluene. Thus, the highest yield was obtained using our original T3P conditions, but it is important to note that other coupling reagents can also be used, in cases where T3P is either unavailable or unsuitable.

The scope of the T3P-meditated DIA conditions described above (Table 1, entry 1) was first tested with regard to the acid coupling partner **2** (Table 2). Note that examples reported in our prior communication are indicated with an asterisk and that the majority of the new examples led to the formation of novel compounds.

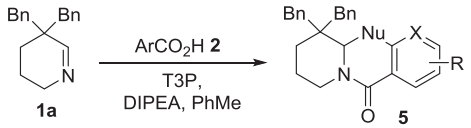
Table 1
Alternative coupling reagents[a]

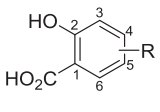
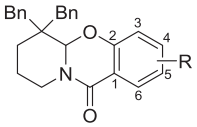
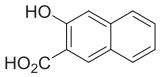
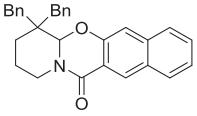
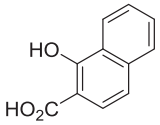
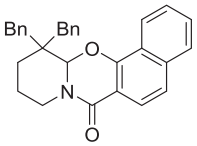
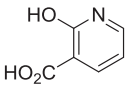
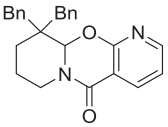
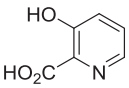
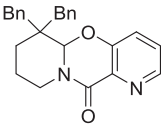
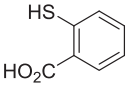
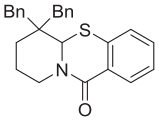
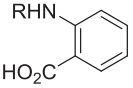
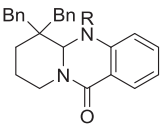


Entry	Coupling agent	Yield[b]
1	T3P	83%
2	CDI	52%
3	DCC	77%
4	EDC	0%

[a] Unless stated, reactions were performed on a 0.1–0.3 mmol scale using imine **1a** (1 equiv), salicylic acid **2a** (1.2 equiv), coupling reagent (1.5 equiv), DIPEA (1.85 equiv) in PhMe at 90 °C for 20 h.
[b] Isolated yields after purification by column chromatography.

Table 2
Benzoic acid scope in DIA with imine **1a**[a]



Entry	Acylating agent	Product	Yield[b]
			
1	**2a** R=H	**5a** R=H	83%*[c,d]
2	**2b** R=3-NO_2	**5b** R=3-NO_2	89%
3	**2c** R=5-NO_2	**5c** R=5-NO_2	91%*
4	**2c**	**5c**	90%*[e]
5	**2d** R=5-Cl	**5d** R=5-Cl	96%
6	**2e** R=4-OMe	**5e** R=4-OMe	82%[f]
7	**2f** R=5-OMe	**5f** R=5-OMe	60%
8	**2g** R=6-OMe	**5g** R=6-OMe	64%[f]
9	**2h** R=4,6-OH	**5h** R=4,6-OH	60%
			
10	**2i**	**5i**	95%*
			
11	**2j**	**5j**	92%*
			
12	**2k**	**5k**	97%*
			
13	**2l**	**5l**	63%
			
14	**2m**	**5m**	96%*[g]
			
15	**2n** R=Me	**5n** R=Me	97%*[c]

(*continued on next page*)