Robust preparation of novel imidazo[5,1-*b*][1,3,4]oxadiazoles†

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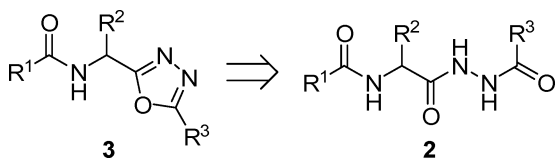
Cyclodehydration of amino acid-derived acyl hydrazide amides 2 to the corresponding oxadiazoles was followed by a second dehydration event, smoothly furnishing the novel imidazo[5,1-*b*][1,3,4]oxadiazole motif 1.

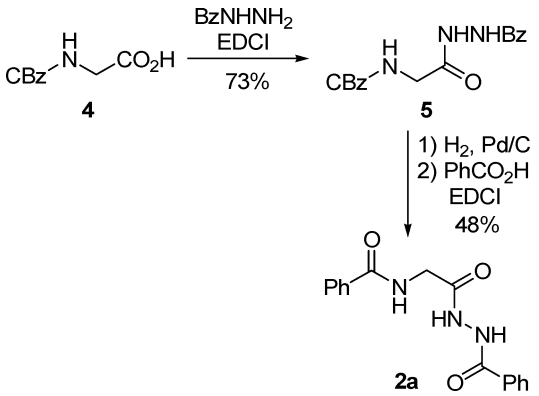
Recently, analysis of a large set of pharmaceutical data supported a general view that lower molecular weight and lipophilicity resulted in a trend toward improved ADME properties.[1] Similarly, it was reported that an increased likelihood of in vivo toxic events could be expected from drug candidates with high lipophilicity.[2] A common strategy for decreasing the lipophilicity in lead structures involves replacing a phenyl ring with a heteroaromatic nucleus. As part of a medicinal chemistry program, we sought to transform a series of *N*-benzyl amides into [1,3,4]oxadiazoles **3**. During the course of the investigation we discovered a facile preparation of a novel heterocyclic motif, which is reported herein.[3–5]



3 **2**

We envisioned that the desired oxadiazolyl amides **3** could be obtained by cyclodehydration of acyl hydrazides **2**. A straightforward preparation of Boc-protected Gly and Ala oxadiazoles had been previously reported.[6] Using a slightly modified procedure, we were able to access the requisite acyl hydrazides (Scheme 1). Hence, conversion of CBz-protected glycine **4** to the benzoyl hydrazide **5**[7,8] using EDCI was followed by deblocking of the carbamate and a second peptide coupling with benzoic acid to furnish the requisite acyl hydrazide **2a**.[9] Boc protection of the amino acid subunit was similarly successful for obtaining acyl hydrazides **2**, obviating the need for hydrogenation (see ESI†).

Cyclodehydration of amino acid-derived acyl hydrazides has been effected with various reagents including thionyl chloride[10] and the Burgess reagent.[11–13] Alternatively, the oxadiazole amides could be obtained from the hydrazide and carboxylic acid partners in one pot with CDI followed by CBr_4/PPh_3,[14] or alternatively in one step using $POCl_3$.[15] However, when $POCl_3$ in refluxing acetonitrile was employed to effect cyclodehydration of **2a**, we observed smooth conversion to a new heteroaromatic product

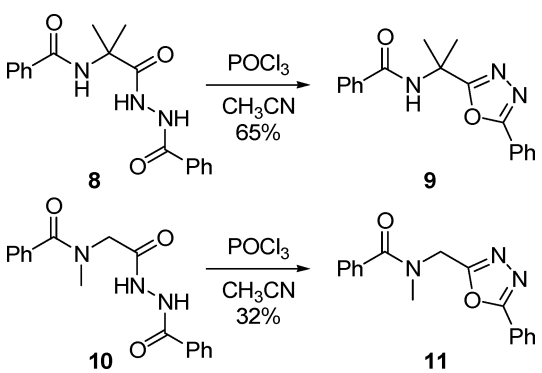


4 **5** **2a**

Scheme 1 Preparation of dibenzoyl hydrazide amide **2a**.

which we considered to be either compound **1a** or **7**, based on LC/MS which suggested that a second dehydration event had taken place.

Two mechanistic possibilities for double dehydration of **2a** were considered (Fig. 1). In scenario A, cyclodehydration to an hydrazido-oxazole **6** would be followed by attack on the carbonyl and dehydration to afford 1*H*-pyrazolo[4,3-*d*]oxazole **7**. In fact, oxazolylamine formation in this manner is precedented, however the amines employed were not contained within a hydrazine motif.[16] Scenario B would proceed as initially envisioned, namely through formation of the oxadiazole amide **3a** which could then proceed to form a novel imidazo-oxadiazole **1a**. Scenario A was ruled out by exposing valine-derived hydrazide **2b** (R^2 = isopropyl), which would be prohibited from undergoing the second dehydration, to $POCl_3$ providing exclusively imidazo[5,1-*b*][1,3,4]oxadiazole **1b** in 73% isolated yield. In addition, when 2-methylalanine was employed as the core subunit in acyclic precursor **8**, only the oxadiazole amide **9** was obtained in 65% yield as cyclodehydration to the imidazo-oxadiazole was precluded by the presence of a quaternary carbon atom (Scheme 2). Similarly,



8 **9** **10** **11**

Scheme 2 Substrates designed to stop at oxadiazole amide.

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† Electronic supplementary information (ESI) available: Full experimental and characterization data for **1a–n**, **2a–n**, and **8–11**. CCDC reference numbers 743852 and 743853. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b916188k

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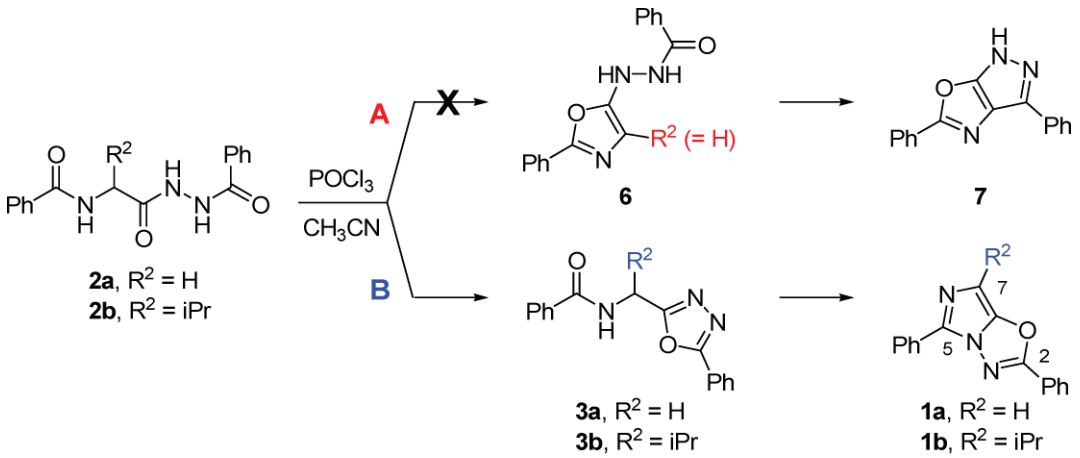


Fig. 1 Possible routes for double dehydration of diacyl hydrazide amides **2**.

methylation of the amide nitrogen as in **10** afforded a substrate unable to participate in the second dehydration event, resulting in exclusive formation of **11**.

Several examples of hydrazides being converted to imidazo-oxadiazole products **1a–k** are shown in Table 1. Gly, Ala, Val, Phg, and Phe at a minimum were tolerated in the core hydrazide. Aromatic or aliphatic functionality could be incorporated at either the 2- or 5-positions of the heterocyclic nucleus. In all cases the process provided >50% isolated yield of the desired imidazo-oxadiazole products. Unambiguous confirmation of the structure was achieved through X-ray crystallographic analysis of **1a** and **1f** (Fig. 2).

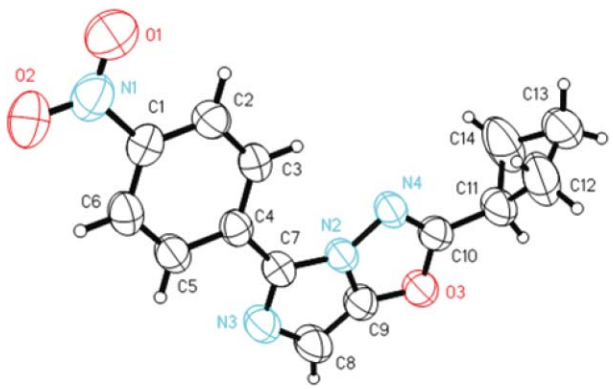
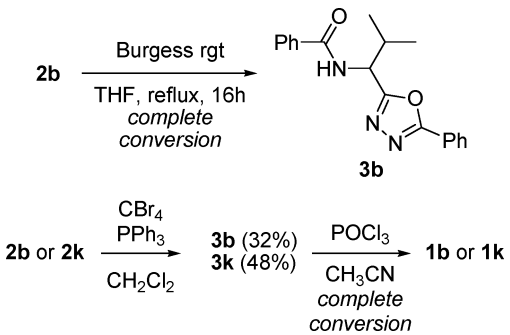


Fig. 2 ORTEP plot of imidazo[5,1-*b*][1,3,4]oxadiazole **1f** with ellipsoids drawn at 50% probability.[17]

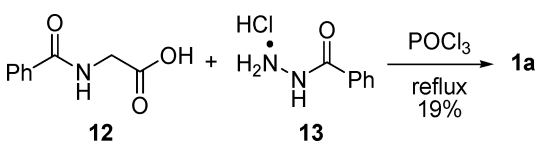
To address the fact that others had previously reported the preparation of oxadiazole amides **3** without mention of a second dehydration event, we first examined the reaction of **2b** under alternate conditions (Scheme 3). Treatment with the Burgess reagent (THF, reflux, 3 h) resulted in *ca.* 25% conversion to amide **3b**, with starting **2b** comprising the balance of material. Extending the time of reaction to 16 h led to complete conversion to amide **3b**. Next, when **2b** or **2k** were reacted under the CBr_4/PPh_3 conditions reported in ref. 8 (with the exception of added CDI), as expected oxadiazole amides **3b** and **3k** were obtained in moderate yield (32% and 48%, respectively). Following



Scheme 3 Dehydration of **2b** and **2k** under alternate conditions.

isolation, the pure amides **3b** and **3k** were completely converted to imidazo-oxadiazoles **1b** and **1k** on treatment with phosphorus oxychloride.

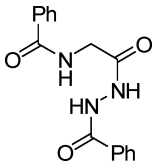
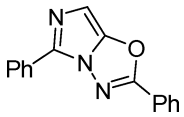
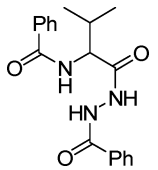
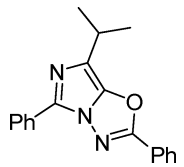
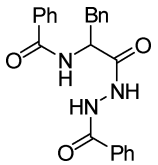
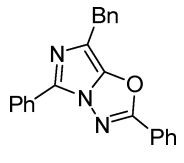
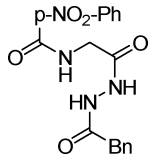
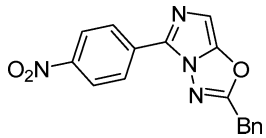
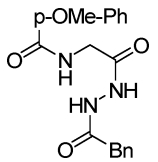
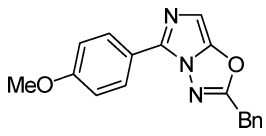
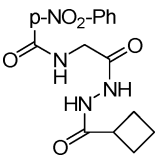
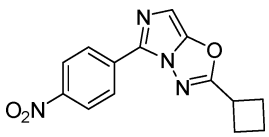
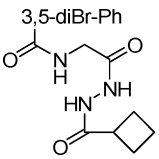
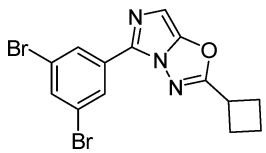
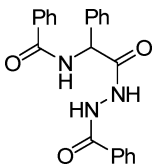
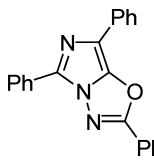
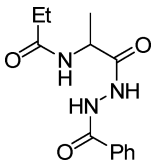
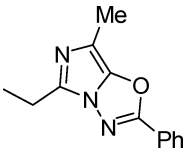
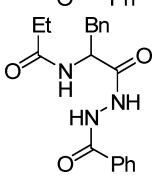
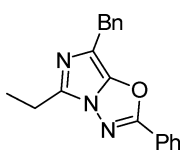
Next, we examined the bimolecular coupling process promoted by $POCl_3$ that was reported to provide the oxadiazole amide as the major product.[7] Hence, hippuric acid **12** and benzhydrazide hydrochloride **13** were combined and refluxed in $POCl_3$ (Scheme 4). After 8 hours, as reported, oxadiazole amide **3a** was determined to be the major product by LC/MS, although we did in fact observe initial formation of the imidazo-oxadiazole **1a** (<10%). In an effort to maximize the amount of **1a** formed, the mixture was refluxed for 2 days resulting in an isolated yield for **1a** of only 19%. Clearly, stepwise formation of diacyl hydrazides **2** was important for obtaining efficient conversion to imidazo-oxadiazoles **1**.



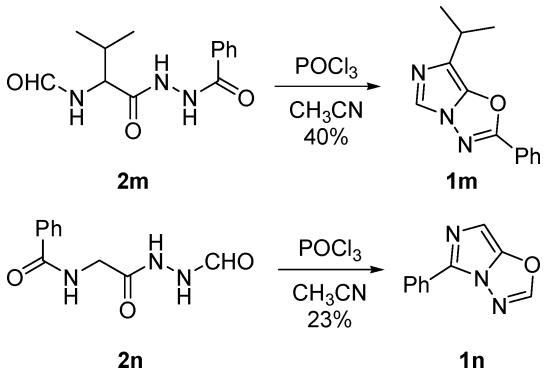
Scheme 4 Examination of bimolecular process to form **1a**.

Finally, we examined whether the carbon substituent at the individual *N*-termini of diacyl hydrazides **2** could be replaced by hydrogen, resulting in lower substitution at positions 2- or 5- of the heterocycle **1** (Scheme 5). Hence, valine-derived formamide **2m** (prepared from **5** as outlined in Fig. 1 using formic acid in

Table 1 Formation of imidazo[5,1-*b*][1,3,4]oxadiazoles **1**[a]

Hydrazide **2**	Imidazo-oxadiazole **1**	Product (Yield%)[b]
		**1a** (76)
		**1b** (73)
		**1c** (80)
		**1d** (65)
		**1e** (76)
		**1f** (50)
		**1g** (80)
		**1h** (62)
		**1j** (76)
		**1k** (67)

[a] Conditions: $POCl_3$, CH_3CN, reflux. [b] Isolated yield.



Scheme 5 Reaction of formamide variants **2m** and **2n**.

place of benzoic) was converted in moderate yield to the desired 5-hydro-imidazo-oxadiazole product **1m**.

To prepare the 2-hydro variant, hippuric acid **13** was coupled with formic hydrazide (EDCI, CH_2Cl_2, 58%) affording formamide **2n**. Double dehydration as before furnished imidazo-oxadiazole **1n** in 23% isolated yield.

In conclusion, as part of an effort to reduce the lipophilicity of a series of *N*-benzyl amides, we targeted oxadiazole amides of type **3**. Formation of the hydrazide of an amino acid such as glycine or valine, and subsequent acylation of both termini allowed for convenient access to the prerequisite cyclodehydration substrates **2**. We were surprised to find that the desired oxadiazole amides were smoothly converted to a novel imidazo[5,1-*b*][1,3,4]oxadiazole motif **1**. Of the previous methods used to prepare oxadiazole amides **2**, in our hands only the bimolecular variant promoted by $POCl_3$ furnished motif **1**, albeit in low yield. Efforts to further elucidate the scope and limitations of this process are currently in progress.

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17 $C_{14}H_{12}N_4O_3$ **1f**: M = 284.28, Triclinic, a = 7.0096(2), b = 7.1705(3), c = 13.7650(5) Å, U = 659.38(4) Å3, T = 298K, space group P-1, Z = 2, 2224 reflections measured, 1519 unique (R_{int} = 0.0140) which were used in all calculations. The final R1 = 0.0422 with wR2 = 0.1275.

