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Stereoselective One-Pot Synthesis of Dihydropyrimido[2,1-*a*]isoindole-6(2*H*)-ones

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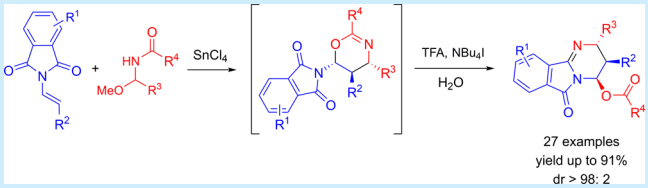
Supporting Information

ABSTRACT: A diastereoselective one-pot synthesis of highly substituted dihydropyrimido[2,1-*a*]isoindole-6(2*H*)-ones containing three continuous stereocenters is reported. The reaction sequence is based on a hetero-Diels−Alder reaction between an enimide and a *N*-acylimine followed by an unprecedented Brønsted acid mediated rearrangement of an intermediate 5,6-dihydro-4*H*-1,3-oxazine to a pyrimido[2,1-*a*]isoindole.



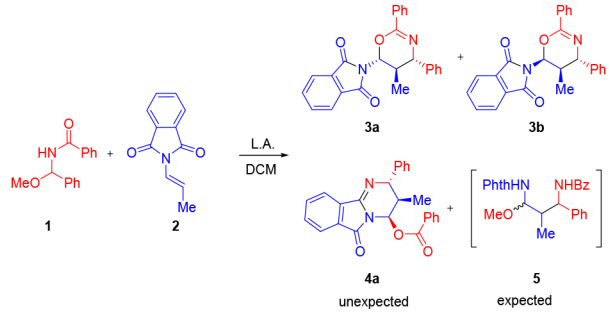
Nitrogen-containing heterocycles are abundant structural motifs in a myriad of natural products and biologically active compounds.[1] Despite all the great achievements in heterocyclic chemistry, there remains a great need for further progress in this area.[2] In this context, the development of new methods for the synthesis of uncommon or to date inaccessible heterocyclic cores is of particular interest.[3]

Herein we report a novel one-pot approach for the preparation of dihydropyrimido[2,1-*a*]isoindole-6(2*H*)-ones. The isoindole motif[4] and especially the pyrimidine core[5] can be found in various natural products and pharmaceutical compounds. On the other hand, dihydropyrimido[2,1-*a*]-isoindoles, formally derived by fusion of the aforementioned heterocycles, are rarely mentioned in the chemical literature.[6] In addition, the biological activity of these tricyclic hetero-aromatics is scarcely studied.[7] Therefore, novel methods for the synthesis of this tricyclic core can provide new opportunities in heterocyclic as well as medicinal chemistry.

The development of the herein described approach toward dihydropyrimido[2,1-*a*]isoindoles started with a serendipitous discovery during our work on the stereodivergent synthesis of 1,3-diamines.[8] Whereas the reaction of enamides[9,10] with acylimine precursors[11,12] in the presence of $BF_3{\cdot}OEt_2$ afforded new *N,O*-acetals, an analogous addition product of type **5** could not be observed with phthaloyl enimide **2** (Table 1).[8]

Instead, three products were obtained in a 1:1:2 ratio and 50% overall yield: the two diasteromeric 5,6-dihydro-4*H*-1,3-oxazines **3a** and **3b** and the dihydropyrimido[2,1-*a*]isoindole-6(2*H*)-one **4a** (entry 1). Formation of the two oxazines products **3a** and **3b** could be rationalized by a [4 + 2]-cycloaddition between the enimide and an in situ formed *N*-acyl imine.[13] Completely unexpected was the tricyclic product **4a**. The structures of **4a** and **3a** could be unambiguously assigned by single X-ray diffraction. The relative configuration of **3b** was determined by NOE experiments in combination with ^3J-coupling constants.[14]

Table 1. Development and Optimization of the Formation of the Dihydropyrimido[2,1-*a*]isoindole-6(2*H*)-one 4



entry	L.A.	additive	selectivity (3a:3b:4a)	yield (%)[a]
1	$BF_3{\cdot}OEt_2$	–	24:28:48	50
2	$SnCl_4$	–	85:15:0	88
3	$SnCl_4$	H_2O	40:16:44	80
4	$SnCl_4$	$TFA_{(aq)}$	7:16:77	71
5	$SnCl_4$	$TFA_{(aq)}$ + nBu$_4$NI	0:<5:>95	89%
6	$SnCl_4$	TFA + nBu$_4$NI[b]	87:13:0	92[c]
7	–	$TFA_{(aq)}$ + nBu$_4$NI	–	decomposition
8	$SnCl_4$[d]	–	–	no reaction
9	$SnCl_4$	$TFA_{(aq)}$[d] + nBu$_4$NI	33:0:67	84
10	$SnCl_4$	$TFA_{(aq)}$ + nBu$_4$NI[d]	0:6:94	76

[a]Overall isolated yield after column chromatography. [b]In the absence of water. [c]Determined by NMR of the crude reaction mixture. [d]With only 0.25 equiv of the respective reagent. L.A. = Lewis acid; Phth = Phthaloyl; TFA = Trifluoroacetic acid, Bz = benzoyl.

Since product **4a** constitutes a very good example for an uncommon or inaccessible heterocyclic core, we investigated this reaction in more detail.

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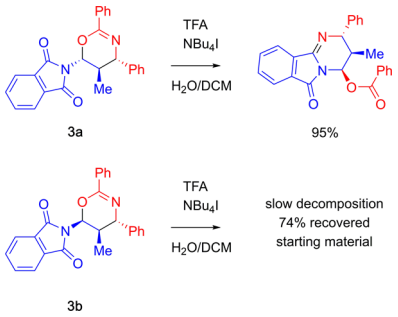
Interestingly, the 5,6-dihydro-4*H*-1,3-oxazines **3a** and **3b** could be obtained exclusively in 88% yield and 81:15 dr in the presence of 2 equiv of $SnCl_4$ as a Lewis acid, followed by a controlled basic aqueous workup at low temperatures (entry 2). Addition of water at room temperature or aqueous workup under acidic conditions led to the formation of varying amounts of tricycle **4a** (entry 3). These results indicate a potential role of aqueous acid in the formation of **4a**. Indeed, the addition of 1 equiv of aqueous trifluoroacetic acid (TFA) after consumption of the enimide led to an increased yield of the desired product **4a** (entry 4). A clean conversion together with an improved yield of **4a** could be achieved through the addition of 1 equiv of tetrabutylammonium iodide (TBAI) (entry 5).[15] The presence of water is crucial for the formation of the dihydropyrimido-[2,1-*a*]isoindole-6(2*H*)-one **4a**. The addition of anhydrous TFA did not furnish the tricyclic product (entry 6). In the absence of a Lewis acid, only decomposition of the starting materials was observed (entry 7). Stoichiometric amounts of $SnCl_4$, aq. TFA, and TBAI are necessary for an efficient transformation (entries 8−10).

As these results indicate a formation of the final dihydropyrimido[2,1-*a*]isoindole-6(2*H*)-one through a rearrangement of the oxazine **3**, we elucidated this potential pathway. Indeed, treatment of 5,6-dihydro-4*H*-1,3-oxazine **3a** with aqueous TFA furnished the expected product **4a** in 95% yield (Scheme 1). Under the same conditions, the reaction of diastereomer **3b** only led to slow decomposition of the starting material. No rearrangement of **3b** to **4a** could be observed.

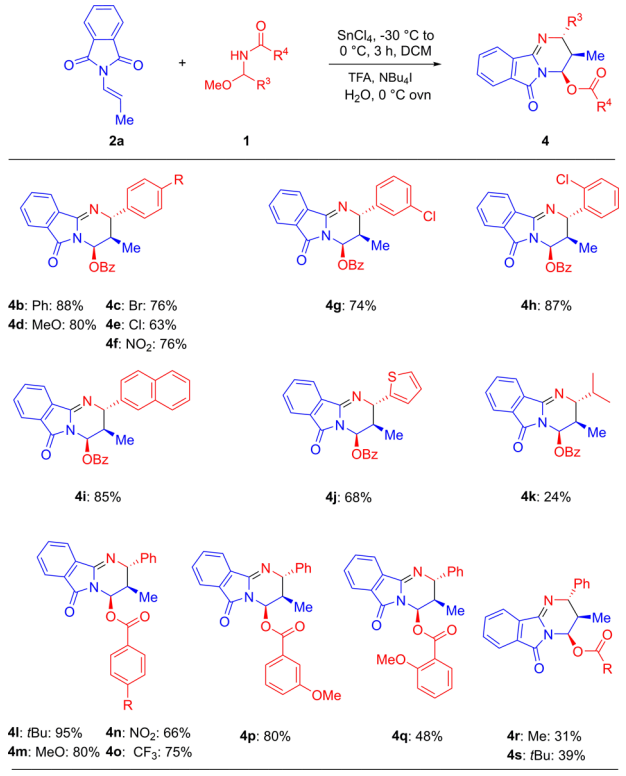
Scheme 1. Formation of Dihydropyrimido[2,1-*a*]isoindole-6(2*H*)-one 4a via Rearrangement of 3a



With the optimized reaction conditions, the scope of this novel method was explored. First, reactions with different *N*-acylimine precursors were investigated (Scheme 2). Aryl- or heteroaryl aldehyde derived *N*,*O*-acetals are suitable substrates, furnishing the desired dihydropyrimido[2,1-*a*]isoindole-6(2*H*)-one **4b−j** in 48−88% and excellent stereoselectivities. The reaction of an isobutyraldehyde-based precursor gave product **4k** in a low yield, albeit with a high degree of diastereoselectivity. In a similar manner, benzamide-derived *N*,*O*-acetals reacted efficiently and the products **4l−q** were obtained in 48−95% yield and >95:5 dr. Reactions of imine precursors bearing an alkylamide moiety furnished the expected products **4r−s** in only 31−43% yield, again with a very high dr.

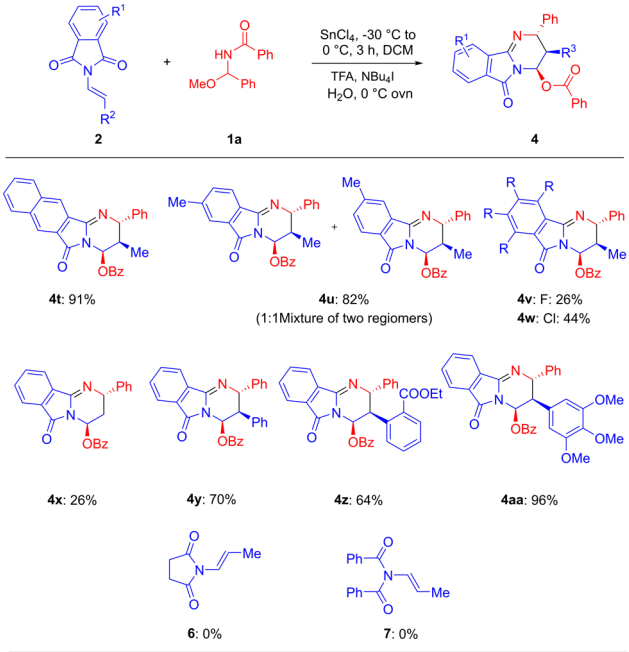
Next, we investigated reactions of various enimides (Scheme 3). *N*-Propenylphthalimides bearing different substituents on the phthaloyl part are compatible with the reaction conditions, and products **4t−w** were isolated in 44−91% yield and excellent diastereoselectivities. Only in the case of the tetrafluoro derivative **4v** a lower yield of 26% was obtained.

Scheme 2. Variation of the Acylimine Precursors[a]



[a]Yields of the isolated products. TFA = Trifluoroacetic acid, Bz = benzoyl.

Scheme 3. Variation of the Enimide[a]



[a]Yields of the isolated products. TFA = Trifluoroacetic acid, Bz = benzoyl.

Reaction of aryl-subtituted *N*-vinylphthalimides furnished dihydropyrimido[2,1-*a*]isoindole-6(2*H*)-one **4y−aa** in 64−70% yield and >95:5 dr. In the case of the unsubstituted *N*-vinylphthalimide, product **4x** was formed in only 26% yield.

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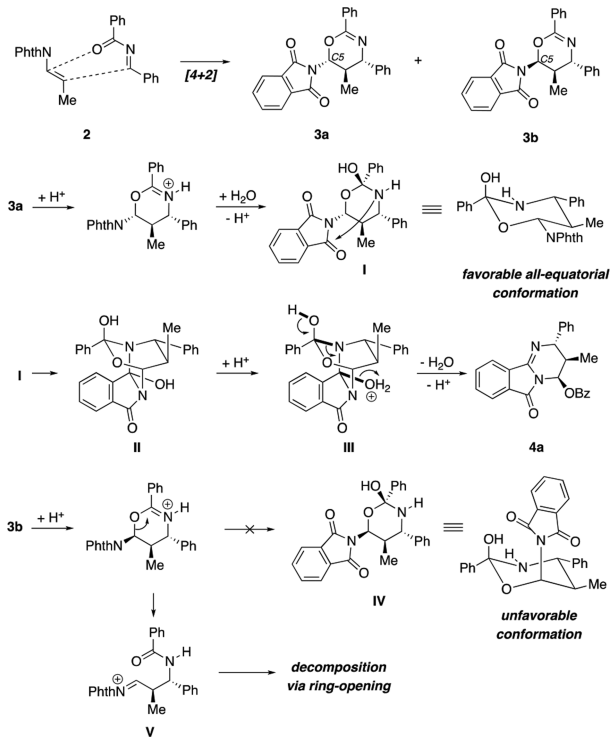
Unfortunately, only *N*-vinylphthalimides are suitable substrates for this transformation. Reaction of the corresponding succinimide-derived enimide **6** or bisenamide **7** did not lead to the formation of the desired pyrimidines.

Based on the observed products and reactivities, we assume the following mechanism (Scheme 4). Reaction of the *N*,*O*-acetal with the Lewis acids leads to the formation of an *N*-acylimine. Reaction of the acylimine with the enimide delivers the two diastereomeric 5,6-dihydro-4*H*-1,3-oxazines **3a** and **3b**. The highly stereoselective formation of diastereomer **3a** can be rationalized by a concerted [4 + 2] cycloaddition between the acylimine as a heterodiene and the enimide as a dienophile proceeding through an endo transition state. The partial loss of stereospecificity implies a bond rotation in an at least partially stepwise process, as it has been observed for polar cycloadditions with acyliminium species.[16] On the other hand, an epimerization after the cycloaddition could also lead to the formation of **3b**. However, we could not detect any epimerization of **3a** under the reaction conditions. Upon addition of a Brønsted acid, protonation of the basic oxazine nitrogen should occur.[17] Subsequent addition of water to the activated C═N bond leads to the formation of intermediate **I**. Intramolecular attack of the oxazine nitrogen to a carbonyl functionality of the imide generates the bicycle **II**. Upon protonation of the newly formed OH group, a fragmentation of **III** affords the final product (**4a**). In the case of oxazine **3a** the addition of water leads to a favorable all-equatorial conformation in combination with the OH group in an axial position (anomeric effect). On the other hand, the addition of water to oxazine **3b** would generate an unfavorable conformation **IV** with the bulky phthaloyl group in an axial position. We assume that, in this case, a ring opening of the oxazine to an acyliminium ion **V** occurs. This reactive species then can undergo various unproductive side reactions, leading to a slow decomposition of **3b**. Although, one could also envision a mechanism through acyclic intermediates, any pathway involving an initial ring opening of the oxazine should proceed through a planar acylimin species (similar to **V**), thereby failing to describe both the retention of stereochemistry at C5 and the preferential rearrangement of **3a**.

Scheme 4. Proposed Reaction Mechanism[a]



[a]Phth = Phthaloyl.

In summary, we have developed a novel one-pot approach for the synthesis of dihydropyrimido[2,1-*a*]isoindole-6(2*H*)-ones. This two-step reaction sequence consists of a polar [4 + 2] cycloaddition between an enimide and a *N*-acylimine and a subsequent, to date unprecedented, acid-mediated rearrangement of the oxazine intermediate. This method enables an efficient and highly stereoselective construction of an uncommon heterocyclic motif and can open new opportunities in heterocyclic or medicinal chemistry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03545.

Syntheses, NMR spectra, and X-ray crystal structures (PDF)

Accession Codes

CCDC 1579081−1579084 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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