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Straightforward Synthesis of Various Chiral Pyrimidines Bearing Stereogenic Center at the C^2 position, Including C-Terminal Peptide Isosters

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Abstract

The present study describes an efficient access to chiral pyridimines from readily available Boc-AA-NH_2 and β-enaminones. This strategy allows the synthesis of a large variety of chiral pyrimidines (18 examples) with good yields from the chiral pool. In the case of peptide isosters, this procedure proved to be highly stereoretentive and paves the way to the construction of C-terminal modified peptidomimetics.

Keywords

Chiral Pyrimidine; Peptide isosters; Heterocycle; β-enaminone; Carboxamide

Introduction

Pyrimidines are widely represented in natural products, synthetic bioactive compounds, materials, and also used in organometallic chemistry (Figure 1).[1-5] Whereas the introduction of chiral centers in heterocyclic compounds (‘escape the flatland’) have been recognized to access a greater chemical space,[6] the introduction (and control) of chirality at the benzylic pyrimidine tertiary centers has been very scarcely studied.[7-8]

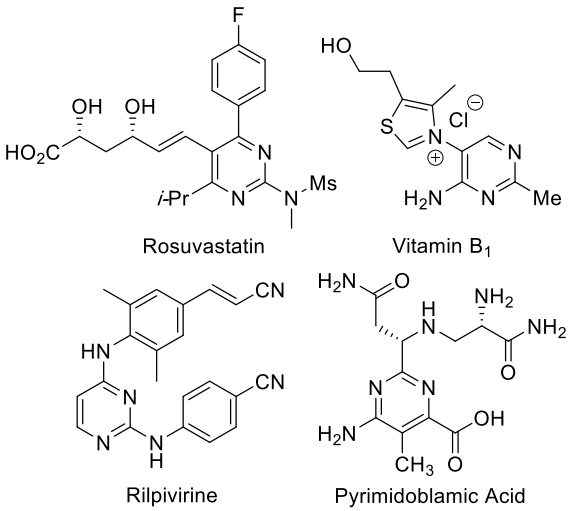
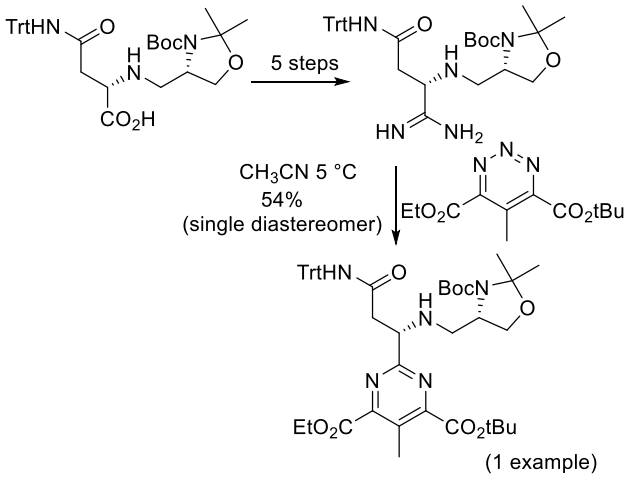


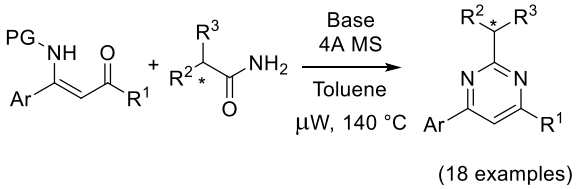
Figure 1: Selected biologically active pyrimidines derivatives

One of the rare methodology that enables the use of the chiral pool was reported by Boger in 2014 as the key step in the synthesis of (-)-pyrimidoblamic acid.[7-8] The pyrimidine is obtained by a Diels-Alder reaction between an electron deficient triazine and an amidine derivative. The synthesis of this amidine residue requires nevertheless five steps from the corresponding carboxylic acid (Scheme 1).

Boger synthesis:



This work:



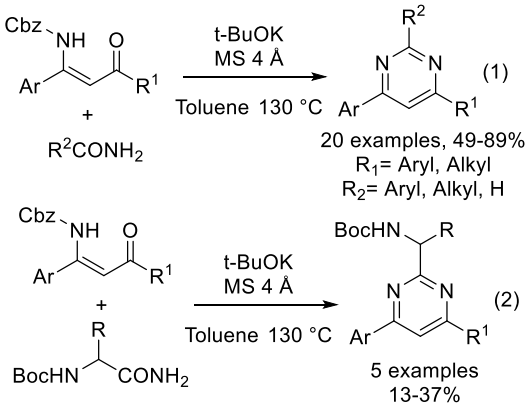
Scheme 1: Methodologies for the synthesis of chiral pyrimidines bearing a stereogenic center at the C2 position.

A more straightforward methodology is thus highly needed in order to expand the structural diversity of these chiral pyrimidines derivatives. This is also particularly desirable as *N*-heterocycles are considered as highly valuable C-terminal peptides isosteres but their access is still challenging. [9-21] We present herein our results in this field.

Results and Discussion

We previously reported the efficient synthesis of di- and tri-substituted pyrimidines from readily available β-enaminones and various carboxamides derivatives (scheme 2, equation 1).[22-23] In the context of the development of original pyrimidylmethylamine (pyrma) ligands and their corresponding Pd(II) complexes, we were keen to apply this methodology to the synthesis of pyrimidines derived from Boc-aminoamides Boc-AA-

NH_2 (scheme 2, equation 2). However, in our original conditions, the yields ranging from 13 to 37% were rather low.[24] We would like in this paper describe an optimization study, the extension of the methodology to other chiral pool derived carboxamides and finally the functionalization of such chiral pyrimidines scaffolds.



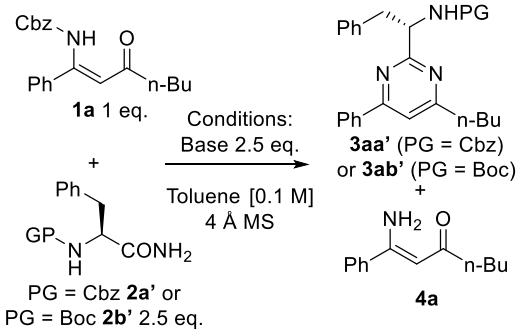
Scheme 2: Application of our original optimized reaction conditions to the synthesis of racemic chiral pyrimidines.

Hoping that Cbz protecting groups may have a greater thermal stability compared to Boc ones in these reaction conditions, the optimization studies were initially carried on the model reaction between Cbz-protected β-enaminone **1a** (Ar=Ph, R^1=*n*-Bu) and both Cbz-Phe-NH_2 **2a'** and Boc-Phe-NH_2 **2b'**. A summary of main results obtained during this optimization study is given in table 1

The reaction was thus first carried out in the presence of *t*-BuOK 2 eq. at 130 °C (Wheaton reactor) but the yield was rather moderate for the use of both Cbz and Boc protected amino-amides (**3aa'**: 25%; **3ab'**: 33%) due to extensive deprotection of the enaminone to give **4a** (entries 1 and 2). Other modifications (T°, solvent, number of equivalents and nature of the base) in the reaction conditions had a negative impact on the isolated yield. The reaction was next run under micro-waves irradiations in order to reduce the reaction time but still maintaining the high reaction temperature

(entries 3 and 4). If the yield was not really improved, we could gratifyingly observe the reduction of the amount of deprotected enaminone **4a**. We were thus keen to re-optimize the reaction parameters under micro-wave conditions. The use of NaH as base was unsuccessful (entries 5 and 6), but notably in the presence of KHMDS the yield of **3aa'** or **3ab'** could be increased to 38% and 52% respectively in the absence of **4a** by-product (entries 7 and 8). Increasing the reaction time to 4 h, the compound **3ab'** could finally be isolated in 60% yield (entry 9).

Table 1

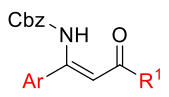


Entry	PG-Phe-NH2	Conditions	Base (2.5 eq.)	**3aa'** or **3bb'** (isolated yield, %)	**4a** (isolated yield, %)
1	**2a'**	Wheaton (130 °C), 3 h	*t*-BuOK	30	32
2	**2b'**	Wheaton (130 °C), 3 h	*t*-BuOK	33	29
3	**2a'**	μW (140 °C), 2 h	*t*-BuOK	24	20
4	**2b'**	μW (140 °C), 2 h	*t*-BuOK	45	17
5	**2a'**	μW (140 °C), 2 h	NaH	44	38
6	**2b'**	μW (140 °C), 2 h	NaH	25	69
7	**2a'**	μW (140 °C), 2 h	KHMDS	38	0
8	**2b'**	μW (140 °C), 2 h	KHMDS	52	10
9	**2b'**	μW (140 °C), 4 h	KHMDS	60	16

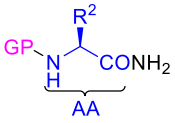
Such harsh reaction conditions could have been detrimental to the stereo-integrity of sensitive AA residues such as phenylalanine. It could be anyway demonstrated that

starting from **1a** and the enantioenriched Boc-Phe-NH_2 **2b'** (er 99:1), the er of the resulting pyrimidine **3ab'** is greater than 97:3, as shown using chiral HPLC by comparison with a racemic sample obtained from racemic Boc-Phe-NH_2 (see SI).

The general scope was next explored with various β-enaminones **1a-d** and a wide range of Boc-AA-NH_2 derivatives **2a'-j'** (Figure 2 and Scheme 3).

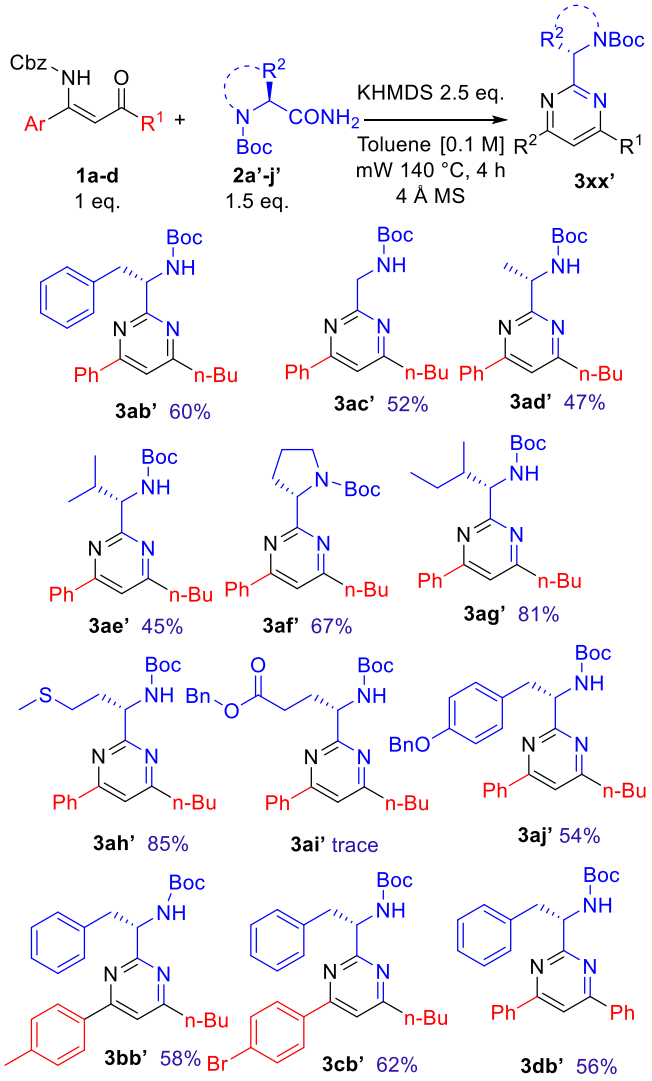


1a : Ar = Ph, R^1 = n-Bu
1b : Ar = *p*-Tol, R^1 = n-Bu
1c : Ar = *p*-BrPh, R^1 = n-Bu
1d : Ar = Ph, R^1 = Ph



2a' : Cbz-Phe-NH_2
2b' : Boc-Phe-NH_2
2c' : Boc-Gly-NH_2
2d' : Boc-Ala-NH_2
2e' : Boc-Val-NH_2
2f' : Boc-Pro-NH_2
2g' : Boc-Ile-NH_2
2h' : Boc-Met-NH_2
2i' : Boc-Glu(Bn)-NH_2
2j' : Boc-Tyr(Bn)-NH_2

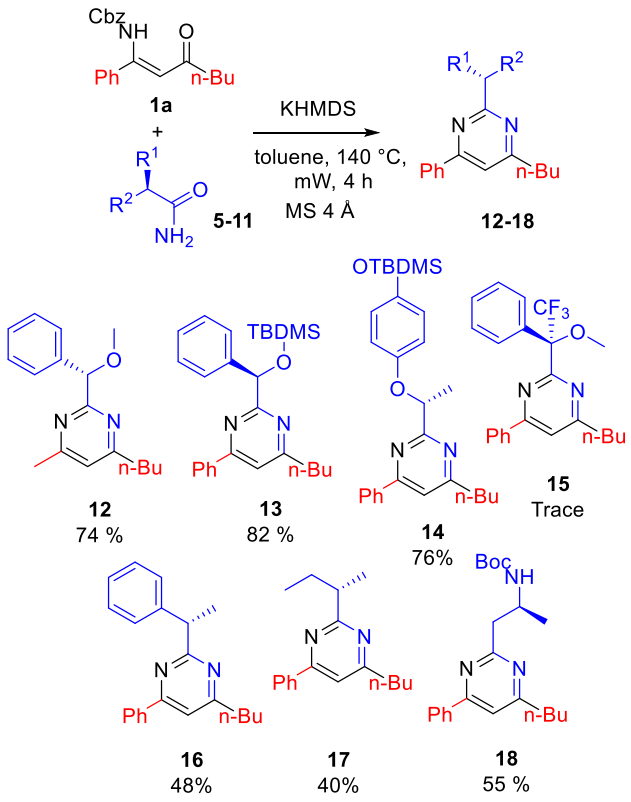
Figure 2: Structure of β-enaminones **1a-d** and carboxamides derived from protected aminoacids **2a'-j'**.



Scheme 3: Scope and limitation for the use of Boc-AA-NH_2.

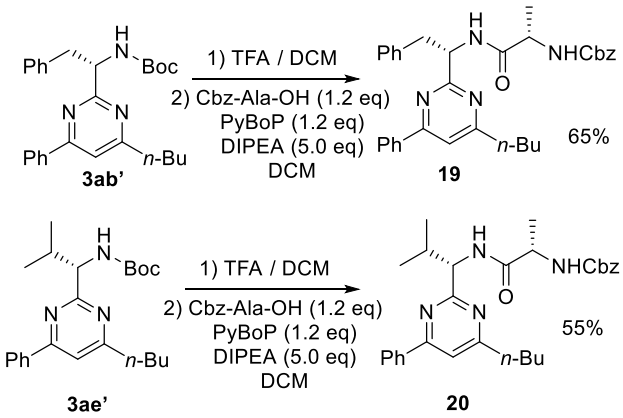
When the AA side chain is aliphatic, the reaction appeared to not be sensitive to steric hindrance as Valine, Proline, Isoleucine derivatives provided the desired pyrimidines **3ae'**, **3af'** and **3ag'** in good yields (45, 67 and 81% respectively). Boc-AA-NH_2 bearing functionalized side-chains (Methionine, Glutamic(Bn) acid and Tyrosine (Bn)) were next investigated: **3ah'** and **3aj'** were obtained in 85 and 54% respectively whereas **3ai'** was only observed as traces due to the lack of solubility of Boc-Glu(Bn)-NH_2 **2j'** in toluene. As previously observed,[22-23] the β-enaminone partner can also be efficiently modified as illustrated with the synthesis of compounds **3bb'**, **3cb'** and **3db'**.

Reaction could then be extended to other α-chiral carboxamides reactants (Scheme 4). Starting from oxygenated ones such as amides **5-7** derived from mandelic and lactic acids, compounds **12-14** have been obtained in 74, 82 and 76% yields respectively. No reaction was nonetheless observed when using more hindered derivatives such as Mosher's acid derivative bearing a quaternary center. It should also be precised that in the presence of non-protected alcohols or phenols, no pyrimidines are observed in these transformations. To note, the presence of heteroatoms in the carboxamide partner is not required as illustrated with the synthesis of pyrimidines **16-17**. Finally, starting from Boc-β-Aminobutyric carboxamide the corresponding pyrimidine **18** could be isolated in 55% yield.



Scheme 4: Scope and limitation for the use of various α-chiral carboxamides.

As previously stated, peptides with *N*-heterocyles C-terminal ends are highly desirable compounds. Indeed, C-terminal modified peptidomimetics have been used to limit the enzymatic degradation and to enhance the bioavaibility.[9-21] To this endeavour, pyrimidines **3ab'** and **3ae'** derived from Phenylalanine and Valine were deprotected in acidic conditions and then coupled to Cbz-Ala-OH in the presence of PyBOP to give the corresponding C-terminal modified pseudo-peptides **19** and **20** in 65 and 55% yields respectively (Scheme 5).



Scheme 5: Synthesis of pseudo-peptide derivatives **19** and **20**.

Conclusion

We have been able to describe a rapid and efficient access to various pyrimidines bearing a stereogenic center in the 2 position from readily available carboxamides issued from the chiral pool (Boc-AA-OH, lactic acid, mandelic acid…). It is worthy to note that this transformation is highly stereoretentive even with the use of highly sensitive amino-acids derivatives. This enables a facile access to C-terminal modified pseudo-peptides and paves the way for the modification of larger peptides and the access to metal bioconjugates.

Experimental

Typical procedure: A dry microwave tube (35 mL) equipped with a magnetic stirrer bar was successively loaded with the corresponding vinylogous amide (1 eq.), the corresponding amide (2.5 eq.) and 4 Å MS (175 mg). The tube was flushed with argon for 3 times. Then, toluene (c= 0.1 M) was added and the mixture was stirred at room temperature. After 5 minutes at room temperature, base (2.5 eq.) was added. The tube was then transferred into the microwave oven, irradiated at 200 W and was stirred at 140 °C for 4 h. The reaction was quenched with an aqueous solution of NH_4Cl (30 mL) and diluted with EtOAc (30 mL). The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, concentrated in vacuo and purification of the crude material via chromatography on silica gel (pentane/EtOAc) afforded the corresponding pyrimidine.

Supporting Information

Supporting Information File 1

General experimental information, synthetic procedures, analytical data and NMR spectra for the reported compounds

compounds.

File Name: Pyrimidines SI

File Format: word

Title: Straighforward Synthesis of Various Chiral Pyrimidines Bearing Stereogenic Center at the C^2 position, Including C-Terminal Peptide Isosters

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