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PADAM reactions of α-aminoaldehydes: Identity of major and minor diastereomers from the Passerini reaction

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ABSTRACT

The Passerini reaction was conducted using *N*-Boc-L-phenylalaninal and a variety of achiral or chiral acids and isocyanides to prepare a library of 27 Passerini products. Reaction diastereoselectivity varied between 1.7:1 and 2.5:1 and in most cases isolation of the individual diastereomers was possible. Passerini products were subjected to a deprotection and acyl migration sequence to give a library of peptidomimetic α-hydroxy-β-acylaminoamides in generally excellent yield. Single crystal X-ray analysis of two of the final products enabled identification of the major diastereomer as having an (*R*) configuration at the newly-formed stereogenic centre, which corresponds to *anti*-Felkin-Anh addition of the isocyanide to the aldehyde.

1. Introduction

Interest in isocyanide-based multi-component reactions (MCRs) has grown exponentially in recent years.[1] Although the Ugi reaction is more widely used, the Passerini reaction has also found use in specific applications. One such application is the preparation of peptidomimetic compounds using the so-called Passerini - amine deprotection - acyl migration (PADAM) strategy.[2] In this case the three-component Passerini reaction is carried out using a protected α-aminoaldehyde **1**, a carboxylic acid **2** and an isocyanide **3**. This is followed by deprotection of the amino group of the Passerini product **4**, and *O*, *N*-migration of the acyl group to give compound **5** (Scheme 1).

A concerted reaction pathway for the Passerini reaction, supported by a gas phase quantum mechanical study, was proposed by Maeda et al.[3] More recently, Ramozzi and Morokuma performed DFT calculations for the Passerini reaction in dichloromethane, and proposed a revised step-wise mechanism (Scheme 2) proceeding through a nitrilium intermediate.[4] It is in this first step leading to the nitrilium intermediate (step A, Scheme 2), that a new stereogenic centre is formed. Formation of the imidate (step B, Scheme 2) is followed by a Mumm rearrangement (step C, Scheme 2), a step that is assisted by an additional carboxylic acid molecule.[3,4] The Mumm rearrangement product gives rise to the Passerini product as shown in step D (Scheme 2).

When starting with chiral starting materials, a degree of diastereoselectivity may be observed in the Passerini reaction.[5] For example, Banfi et al. determined the reaction diastereoselectivity when using six different N-protected α-aminoaldehydes in combination with achiral isocyanides and chiral or achiral carboxylic acids.[2a] They found that the diastereoselectivity varied between 1.3:1 and 2.5:1. Other workers using the PADAM approach have reported similar diastereoselectivities in their Passerini reactions,[6] but in none of these cases was the identity of the major and minor diastereomer determined.

Our own interest in this chemistry stems from our use of the PADAM approach, starting from *N*-Boc-phenylalaninal (**1**, R = Bn), for the preparation of compounds such as **6** (Fig. 1), which was found to exhibit activity as an HIV-1 protease inhibitor.[7] All but one of the FDA-approved HIV-1 protease inhibitors have been designed as peptidomimetic transition-state mimics to resemble the tetrahedral intermediate formed during peptide bond cleavage.[8] A common cleavage site for HIV-1 protease is adjacent to phenylalanine,[9] thus most inhibitors have a benzyl and hydroxyl group in close proximity, generally adjacent to each other. Based on differences in the relative stereochemistry between the adjacent benzyl

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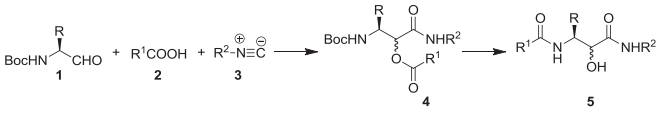
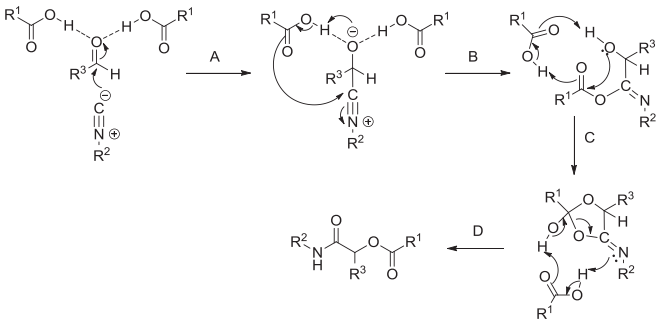


Scheme 1. PADAM strategy.



Scheme 2. Revised mechanism of the Passerini reaction after Ramozzi and Morokuma.[4]

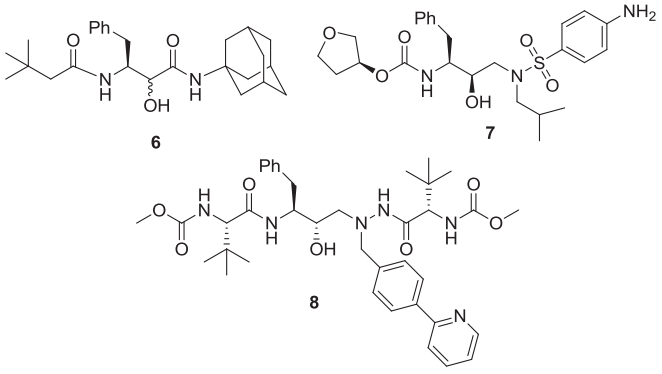


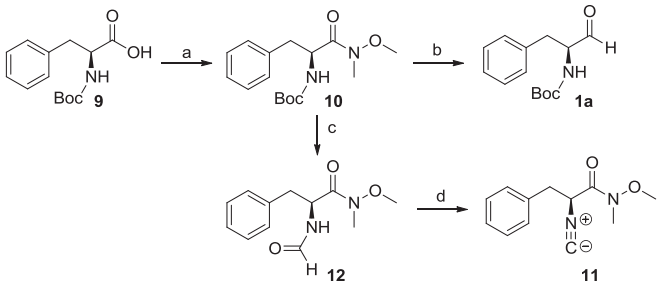
Fig. 1. Our previously identified HIV-1 protease inhibitor **6** and FDA-approved HIV-1 protease inhibitors amprenavir **7** and atazanavir **8**.

and hydroxyl groups in FDA-approved HIV-1 protease inhibitors such as amprenavir **7** and atazanavir **8** (Fig. 1), we were interested to determine whether the relative stereochemistry of our major diastereomer corresponded to that of amprenavir or atazanavir. Thus, we undertook to investigate the Passerini reaction between *N*-Boc-phenylalaninal (**1a**, R = Bn) and various isocyanides and carboxylic acids in order to determine the reaction diastereoselectivity and the configurations of the resulting major and minor diastereomers.

2. Results and discussion

The aldehyde component used in all the Passerini reactions was *N*-Boc-L-phenylalaninal (**1a**), which was prepared from *N*-Boc-L-phenylalanine (**9**) via Weinreb amide **10** (Scheme 3), as previously described.[10] Chiral isocyanide **11** was also prepared from **9** by formylation to give **12**, followed by dehydration (Scheme 3) while compound *ent*-**11**, was prepared in an analogous fashion from *N*-Boc-D-phenylalanine. All other isocyanides and carboxylic acids used were commercially available.

Results from the Passerini reaction of the different substrates are shown in Table 1. In most cases the yield of the Passerini reaction was excellent. In line with previous work done on these kinds of substrates, the diastereomeric ratio was found to range between



Scheme 3. Preparation of starting materials. *Reagents and conditions*: (a) i. 1.2 eq.CDI, CH_2Cl_2, rt; ii. 1.2 eq. *N,O*-dimethylhydroxylamine HCl; (b) 1.5 eq. $LiAlH_4$, THF, 0 °C; (c) excess HCOOH, Ac_2O; (d) PPh_3, CCl_4, DIPEA, CH_2Cl_2, rt.

1.34:1 and 2.49:1. The two best diastereoselectivities were obtained for compounds **33** and **39**, where the chiral acid *N*-Boc-L-phenylalanine (**9**) was used. Thus, *N*-Boc-L-phenylalaninal (**1a**) and *N*-Boc-L-phenylalanine (**9**) appear to represent a matched pair, while isocyanide *ent*-**11** did not impact negatively on diastereoselectivity. The two poorest diastereoselectivities were observed for compounds **35** and **36**, where the chiral isocyanide **11** was used. Thus, *N*-Boc-L-phenylalaninal (**1a**) and isocyanide **11** appear to represent a mismatched pair.

However, the fact that a roughly 2:1 ratio was obtained even when using achiral carboxylic acids and isocyanides shows that the dominant factor controlling diastereoselectivity is the stereochemistry of the aldehyde. Interestingly, when compound **13** was prepared by means of microwave irradiation using a general method described by Barreto et al.[11] all diastereoselectivity was lost, and equal amounts of the two diastereomers were obtained.

Passerini products **4** (**13**–**33**) were then subjected to deprotection and acyl migration to give rise to PADAM products **5** (Table 2). Where possible, the diastereomeric Passerini products were separated by means of semi-preparative HPLC to give a pure major (**4A**) and minor (**4B**) diastereomer prior to deprotection and migration to give **5A** and **5B**, respectively. As expected, no racemisation of the stereogenic centres was observed during the deprotection-migration sequence. Good to excellent yields were obtained for all but a few examples in the cyclohexyl isocyanide series.

Of interest to us was the trend that the minor diastereomers were generally less soluble than the major diastereomers for both the Passerini and PADAM products. In addition, although rotamers can often be observed for compounds containing amide bonds, our NMR spectroscopic data showed that the minor diastereomers were far more likely to show the presence of rotamers than the major diastereomers. For example, in the ^{13}C NMR spectrum for minor diastereomer **47B**, two signals each were observed for most of the carbon atoms present in the compound, while for major diastereomer **47A**, the expected number of signals was observed. This effect may also be the result of intramolecular hydrogen bonding through formation of a six-membered ring that may be more energetically favoured in one diastereomer over the other.

None of the separated Passerini diastereomers (**4A** or **B**) proved amenable to single crystal X-ray analysis. However, the PADAM product **40B**, obtained from minor diastereomer **13B** after deprotection and acyl migration, was crystalline and was shown by single crystal X-ray diffraction to have the (*S*)-configuration at the newly-formed C-2 stereogenic centre (Fig. 2). Similarly, PADAM product **56A**, obtained from major diastereomer **29A**, was found by single crystal X-ray diffraction to have the (*R*)-configuration at C-2 (Fig. 3). Based on these results, obtained from two different isocyanide series, we propose that the same major and minor diastereomer is seen for all compounds synthesised. This is supported by the ^{13}C