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Enantioselective synthesis of aroylalanine derivatives

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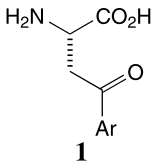
Abstract—In this paper we report the development of a highly enantioselective method for the synthesis of aroylalanines. The approach described employs a protected 2-amino-4-bromopent-4-enoic acid, generated via the asymmetric phase-transfer catalyzed alkylation of a glycine imine, as a key intermediate. Suzuki coupling with an aryl boronic acid followed by ozonolysis of the resulting styrene provides efficient access to the aroylalanine derivatives. The utility of this methodology is illustrated by the synthesis of L-kynurenine along with several aroylalanine inhibitors of the kynurenine pathway.

Aroylalanine derivatives **1** constitute an interesting group of α-amino acids that have attracted considerable interest in recent years. Much of this interest has arisen as a consequence of studies into the kynurenine pathway,[1,2] a process that starts with the oxidative cleavage of the essential amino acid L-tryptophan to give kynurenine **1a**. This pathway appears to play an important role in a variety of fundamental biological processes, including neuronal excitability, antioxidant status, and cell growth/cell division. The need to study this pathway in more detail, coupled with the recognition that it could offer a means of treating a wide variety of disorders,[1] has led to significant interest in the synthesis of kynurenine and related aroylalanine derivatives.[2]



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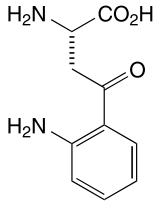
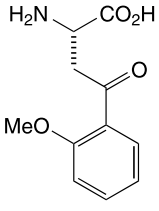
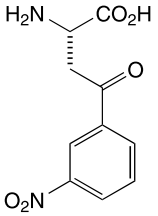


1a



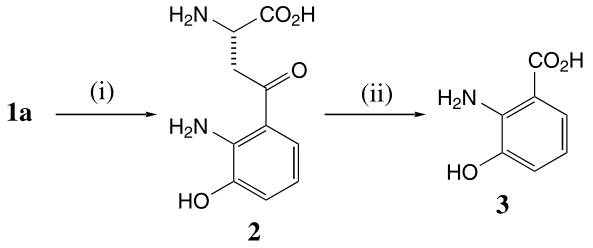
1b



1c

In recent years it has been shown that a number of aroylalanine derivatives are able to act as selective inhibitors of enzymes involved in this pathway. For example it has been demonstrated that *o*-methoxybenzoylalanine **1b** preferentially inhibits kynurenine 3-hydroxylase and *m*-nitrobenzoylalanine **1c** is an inhibitor of kynureninase (Scheme 1).[2p,q,s,3] This highlights the need for synthetic methods that allow efficient access to aroylalanine derivatives, and in this paper we report the development of such an approach and its application to the enantioselective synthesis of compounds **1a**–**c**.

Over the past few years we[4] have been concerned with the development and application of the asymmetric phase-transfer catalyzed alkylation of glycine imine **4**.[5,6] In particular we have focussed on alkylation conditions that involve the use of aqueous hydroxide at room temperature. These reaction conditions have proved extremely convenient to use[4,7] and are compatible with a wide range of alkylating agents, however we have found that alkylations involving α-haloketones (e.g. α-bromoacetophenone, Scheme 2) generally result in



Scheme 1. (i) Kynurenine 3-hydroxylase; (ii) kynureninase.

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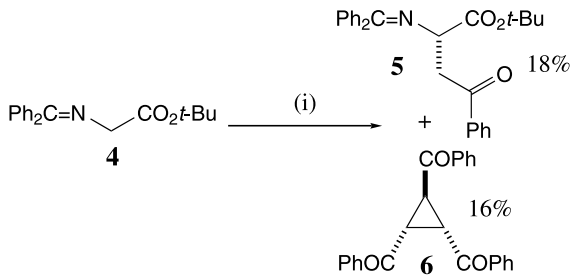
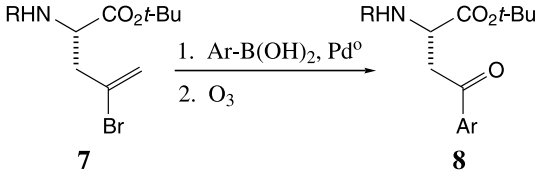


Scheme 2. (i) α-Bromoacetophenone, 9 M aq. KOH, PhMe, *O*-benzyl-*N*-9-anthracenylmethyldihydrocinchonidinium bromide **9c** (10 mol%), rt.

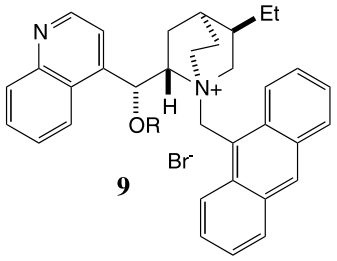


Scheme 3.

low yields of the desired product **5**. This is primarily because the α-bromoketone is prone to hydrolysis and also readily participates in a base-mediated self condensation leading to the formation of the cyclopropyl ketone by-product **6**.[8] Recently it has been shown that careful optimization of the reaction conditions can minimize these problems and this has enabled an enantioselective synthesis of the highly fluorescent amino acid 6-(2-dimethylaminonaphthoyl) alanine to be developed.[9] We have been investigating an alternative solution to this problem, one which avoids the involvement of α-haloketones, and which allows installation of the aryl moiety at a relatively late stage, thus facilitating the synthesis of a range of aroylalanine derivatives from an advanced intermediate.

Our approach is centred on the potential utility of 2-amino-4-bromopent-4-enoic acid derivatives **7** as direct precursors to aroylalanine derivatives **8**. We envisaged that the transformation of **7** into **8** should be possible via Suzuki coupling[10] followed by oxidative cleavage (Scheme 3), and that this chemistry should be compatible with a wide variety of aryl groups.

For this strategy to be successful, efficient access to amino acid derivatives **7** is required. To this end we examined the utility of the asymmetric PTC alkylation of imine **4** with 2,3-dibromopropene. Initially we employed the quaternary ammonium salt **9a** as the precatalyst[4d,e] in the asymmetric alkylation reaction. This salt was chosen as it usually leads to very high levels of enantioselectivity and favours formation of the L-amino acid stereochemistry. Unfortunately, in this instance, although the desired stereoisomer was favoured, variable levels of enantioselectivity (e.e.'s 41–60%) were obtained. Under the alkylation conditions the precatalyst **9a** is converted into the *O*-alkyl derivative **9b**. In most alkylations of this type this does not significantly effect the enantioselectivity of the reaction,[4d] however in this case it appears that the latter salt is relatively insoluble in the organic reaction phase (PhMe). This results in a reduction in the effective concentration of the catalyst, which in turn results in a lowering of the enantioselectivity. To overcome this problem we screened a range of different dihydrocinchonidine-derived salts[4a] and found that use of the *O*-benzyl derivative **9c** resulted in high levels of enantioselectivity (93–95% e.e.).

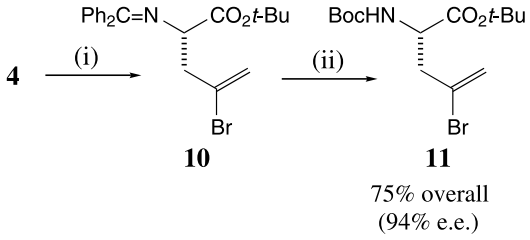


a, R = H
b, R = $CH_2C(Br)=CH_2$
c, R = CH_2Ph

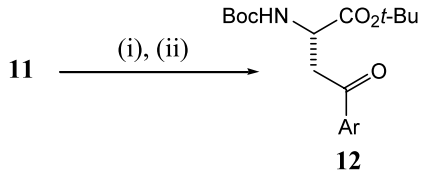
Thus, asymmetric alkylation of imine **4** with 2,3-dibromopropene followed by imine hydrolysis and *N*-protection gave the amino acid derivative **10**[11] in good overall yield (Scheme 4). Using this approach, the enantiomeric excess of crude **11** was found to be 94%.[12]

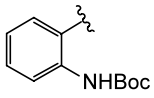
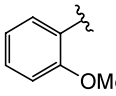
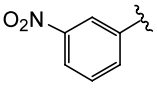
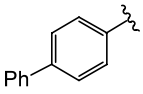
Suzuki couplings involving amino acid **11** gave excellent yields under standard conditions, and simple ozonolysis followed by reductive work-up then gave the protected aroylglycines **12** (Scheme 5). As can be seen this two-step sequence is compatible with both electron rich and electron deficient aryl functions and *ortho*-substituents in the aromatic ring do not appear to cause any problems. HPLC analysis on selected products established that this sequence does not result in any loss of enantiomeric excess, and thus confirmed that this is a highly enantioselective route to protected aroylalanines.

In order to complete the synthesis of compounds **1a**–**c**, we investigated a number of deprotection methods.[2u,13] It was found that this could best be achieved by heating intermediates **12** in a mixture of chloroform and TFA. Purification by ion-exchange chromatography then provided L-kynurenine **1a**, L-*o*-methoxybenzoylalanine **1b** and L-*m*-nitrobenzoylalanine **1c** in good overall yield (Scheme 6). Compounds **1a**–**c** had spectroscopic data in agreement with that previously reported,[2l,n,p] confirming their structural assignment.



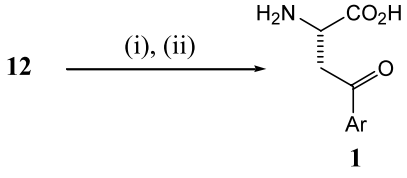
Scheme 4. (i) 2,3-Dibromopropene, 9 M aq. KOH, PhMe, CH_2Cl_2, *O*-benzyl-*N*-9-anthracenylmethyldihydrocinchonidinium bromide **9c** (10 mol%), rt; (ii) 15% aq. citric acid, THF, rt; Boc_2O, Et_3N, rt.



Entry	Ar	% Yield (12)*
a		84
b		87
c		96
d		58
e		86

* overall yield after purification

Scheme 5. (i) Ar-B(OH)$_2$, Pd(PPh$_3$)$_4$, 2 M aq. Na$_2$CO$_3$, PhMe, EtOH, reflux; (ii) O$_3$, CH$_2$Cl$_2$, −78°C; Et$_3$N, rt.



Substrate	Product	% Yield (1)
12a	1a	62
12b	1b	60
12c	1c	68

Scheme 6. (i) CF_3CO_2H, $CHCl_3$, reflux; (ii) ion-exchange chromatography (Dowex 50WX8-200).

In conclusion, we have developed an efficient and highly enantioselective method for the preparation of aroylalanine derivatives. We anticipate that this chemistry will prove useful in the search for novel inhibitors of the kynurenine pathway and further developments in this area are currently under investigation.

Acknowledgements

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12. Enantiomeric excess was determined by HPLC (Chiralcel OD-H, 99.5% hexane/0.5% IPA, 0.5 ml/min) using racemic **11** (generated using n-Bu_4NBr as the PTC) as a control. Retention times observed were 10.6 min (L-isomer) and 12.6 min (D-isomer).
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