Enantioselectively functionalised phenytoin derivatives by auxiliary-directed N to C aryl migration in lithiated α-amino nitriles

Josep Mas-Roselló, Mary Okoh and Jonathan Clayden

Lithiation of N'-arylureas derived from amino nitriles incorporating a (1R, 2R)-2-aminocyclohexanol chiral auxiliary leads to diastereoselective migration of the aryl ring to the position α to the nitrile. The resulting N'-lithiated ureas undergo spontaneous cyclisation to iminohydantoins, which may be hydrolysed to give chiral 5,5-diarylhydantoins related to phenytoin, in enantioenriched form.

α-Aryl quaternary amino acid motifs form components of several biologically active compounds, especially in the form of their 5,5-diaryl hydantoin derivatives (Scheme 1a).[2b,3] In addition to this, the role of this motif in controlling the conformation of peptidomimetics[3] makes the stereoselective α-arylation of amino acids an important synthetic challenge. A number of approaches have been taken towards this aim, typically using S_N Ar reactivity of highly electrophilic aryl rings or arynes towards nucleophilic enolate equivalents.[2b,3]

Nonetheless, the stereoselective arylation of phenylglycine and other arylglycines[4] remains an unsolved problem, with the few reported routes to chiral α-aryl glycines being characterized by diminished stereoselectivity or reactivity relative to their α-alkyl tertiary amino acid counterparts.[3-5]

One approach to the arylation of α-amino acids entails the use of an unusual electronically unactivated Smiles-like rearrangement that takes place within anionic or organometallic derivatives of N'-aryl ureas.[2b,3a,3b,6,7] We showed for example that the urea derivatives of amino nitriles 1, when deprotonated, undergo racemic intramolecular N'→C aryl transfer to 2, leading to arylated iminohydantoins 3 after spontaneous cyclisation.[7] Similar rearrangements of aminomides and aminoesters have been rendered asymmetric by the use of chiral auxiliaries[2b,3a] or chiral memory,[3b] but these reactions failed to give products when highly hindered substrates such as phenylglycine were used as starting materials. We envisaged that the incorporation of a chiral auxiliary as R^2 in phenylglycine-derived amino nitriles 1 having an aromatic substituent R^3 might enable a diastereoselective arylation of ureas 1, thereby giving access to enantioselectively enriched iminohydantoins 3 (Scheme 1b).[3b]

These are immediate precursors of both hydantoins 4 and amino acids 5, which may be revealed by hydrolysis.[9] The method would furthermore be independent of the configuration of the amino acid moiety, making it particularly applicable to non-proteinogenic amino acids such as phenylglycines.

--

Scheme 1. (a) Bioactive α-aryl quaternary amino acids and hydantoin derivatives; (b) A published method for the synthesis of α-aryl quaternary amino acids and hydantoins by intramolecular arylation of aminonitrile ureas 1.
In order to explore this proposal with an amino-acid derivative bearing 'unnatural' substituents, a trial urea \(6a\) was made as a 1:1 mixture of diastereoisomers from optically pure (R)-1-(4-methoxyphenyl)ethylamine in a 3 step sequence involving a Strecrker reaction.\(^{[10]}\) N-Phosgenation of the resulting aminonitrile, and urea coupling with \(N\)-methylalanilne. The generality and simplicity of this Strecrker approach to the starting materials illustrates a further advantage of using amino nitriles substituted at this position. Initial optimisation of the arylation reaction was carried out using this furan-substituted nitrile \(6a\) (Table 1). Several different bases deprotonated the starting material \(\alpha\) to the nitrile function and promoted rearrangement and cyclisation to the \(\alpha\)-arylated iminohydantoin product \(7a\), generally in good yield. sec-BuLi gave poor selectivity (entries 1,2), and among the other bases LDA performed best, with optimal yield and selectivity being obtained in the absence of an additive: entry 7 shows a yield of 93% with 77:23 dr.

**Table 1.** Optimisation of reaction conditions using \(6a\).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base(^{[a]})</th>
<th>Additive</th>
<th>(t/)h, (T/)°C</th>
<th>(7a) yield (%) (dr)(^{[b]})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>sec-BuLi</td>
<td>DMPU(^{[d]})</td>
<td>16, -50</td>
<td>88 (57:43)</td>
</tr>
<tr>
<td>2</td>
<td>LDA</td>
<td>DMPU(^{[d]})</td>
<td>6, 0</td>
<td>90 (67:33)</td>
</tr>
<tr>
<td>3</td>
<td>LDA</td>
<td>LiCl(^{[n]})</td>
<td>6, 0</td>
<td>83 (74:26) (^{[f]})</td>
</tr>
<tr>
<td>4</td>
<td>LDA</td>
<td>LiCl(^{[n]})</td>
<td>3, rt</td>
<td>91 (76:24)</td>
</tr>
<tr>
<td>5</td>
<td>LITMP</td>
<td>LiCl(^{[n]})</td>
<td>3, rt</td>
<td>76 (75:25)</td>
</tr>
<tr>
<td>6</td>
<td>LiHMDS</td>
<td>LiCl(^{[n]})</td>
<td>16, rt</td>
<td>90 (74:26)</td>
</tr>
<tr>
<td>7</td>
<td>LDA</td>
<td>-</td>
<td>3, rt</td>
<td>93(^{[g]}) (77:23)</td>
</tr>
<tr>
<td>8</td>
<td>KHMD5</td>
<td>-</td>
<td>12, rt</td>
<td>86 (67:33)</td>
</tr>
</tbody>
</table>

\(^{[a]}\) Base (2.0 equiv. added to \(6a\) in THF). \(^{[b]}\) Yield and dr determined by \(^1\)H NMR of the crude reaction mixture using hexamethylbenzene as internal standard. \(^{[c]}\) Absolute configuration of new stereogenic centre not determined. \(^{[d]}\) DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone, 10% v/v. \(^{[e]}\) 4 equiv. of dry LiCl added. \(^{[f]}\) \(7a\) recovered as a 50:50 mixture of diastereoisomers. \(^{[g]}\) Isolated yield of a mixture of diastereoisomers in a 65:35 ratio.

The next challenge was to increase the diastereoselectivity of the reaction. A series of substrates \(6b-6e\) were made as diastereoisomeric mixtures from enaniopure primary amines (H\(_2\)N–R\(^{2}\); highlighted in green) by the Strecrker route used for \(6a\) (Scheme 2). Substrates \(6b-c\) containing chiral amines with additional metal-coordinating sites\(^{[11]}\) were detrimental for both selectivity and yield. Protection of the free hydroxyl group of \(6c\) in the form of the \(O\)-tert-butyldimethylsilyl derivative \(6d\) led to an increase in dr. Finally, the less flexible trans-2-aminocyclohexanol-derived substrate \(6e\) turned out to be the most selective by far, giving the iminohydantoin \(7e\) with a diastereoselectivity of >95:5. Repeating the reaction with both diastereoisomers individually gave the same selectivity. Trans-2-aminocyclohexanol has been used as a chiral auxiliary or chiral ligand in a number of other reactions,\(^{[12]}\) and both enantiomers are commercially available and equally accessible on scale from amination of the corresponding meso epoxide.\(^{[12,13]}\) The auxiliary may be easily removed under acidic conditions by dehydration – enamde hydrolysis.

![Scheme 2. Screening chiral amines as auxiliaries. 2 equiv LDA used unless otherwise indicated. Diastereomeric ratios determined by \(^1\)H NMR of crude reaction mixtures. \[a\] Absolute configuration of new stereogenic centre not determined. \[b\] 3 equiv LDA. \[c\] Yield from diastereoisomer 1. \[d\] Absolute configuration of \(7e\) (Ph ring migrates) assigned as shown by analogy to \(9b\) (see below). \[e\] Yield from diastereoisomer 2.](image)

Extension of the highly diastereoselective rearrangement of \(6e\) to other substrates would constitute a method for the synthesis of enantiomerically enriched 5,5-diaryl hydantoin related to the anti-convulsant drug phenytoin, selectively functionalised on one of the two phenyl rings.\(^{[14]}\) Such enantioselectively functionalised structures have found extensive in explorations of mechanisms of biological oxidation of this drug, but have been previously accessible in enantipure form only by resolution.\(^{[15]}\) To explore the application of the diastereoselective arylation to the asymmetric synthesis of phenytoin derivatives and other chiral 5,5-diarylhydantoins, we made a series of ureas \(8a-e\) bearing the optimal silylated (1R, 2R)-aminocyclohexanol auxiliary using the Strecker-type protocol employed for the synthesis of \(6a-e\) (see supporting information).

A pair of diastereoismeric 4- and 4'-methylated phenytoin derivatives was made by migrating respectively a phenyl group to the \(\alpha\)-position of the \(p\)-tolyl substituted urea \(8a\) and a \(p\)-tolyl group to the \(\alpha\)-position of the phenyl substituted urea \(8b\). Both reactions proceeded with excellent diastereoselectivity, and gave phenytoin derivatives \(9a\) and \(9b\) of opposite absolute configuration at the quaternary centre. On the basis that the new stereogenic centre of \(9b\) has \(S\) configuration (see below) we deduce that the (1R, 2R)-aminocyclohexanol induced migration to the \(S\) face of the intermediate enolate. The phenyl group migrated in this intramolecular \(S\_Ar\) reaction
somewhat more readily than the p-tolyl group, which required DMPU as co-solvent and heating to +40 °C to reach completion.

A second pair of diastereoisomeric fluorinated phenytoin derivatives was made by migrating either the 4-fluorophenyl group of 8c or the phenyl group of 8d, giving the enantioselectively fluorinated derivatives 9c and 9d. Again the substituted 4-fluorophenyl ring required more forcing conditions to migrate.

This diastereoselective arylation is of particular strategic value for the synthesis, in an enantioselective manner, of diaryl glycin derivatives in which the aryl rings are only minimally different, and would therefore be impossible to resolve using standard techniques. Illustrating this point, migration of the 2,3,4,5,6-pentadeuterophenyl ring to the phenyl-bearing nitrile substrate 8e gave a product in which the phenytoin moiety is enantioselectively deuterated in only one of the two rings.[18] in 52% yield with 95:5 e.r. The absolute configuration of (S)-11b was determined by comparison of its HPLC retention time on a chiral stationary phase with that of an authentic sample[17] (see SI for further details).

The mechanism by which the intramolecular arylation takes place is an unactivated Smiles-like rearrangement[18] induced by the well-defined conformation[19] of the N-aryl urea.[20] This family of reactions do not require electron-withdrawing groups for success[3a,3b,6a,6b,7,9] and appear to proceed by a single step pathway without a Meisenheimer intermediate.[20,21]

In summary, the diastereoselective intramolecular C-arylation of α-amino nitrile derivatives of phenylglycines gives, with high levels of stereoselectivity, α,α-diarylated hydantoin derivatives. The reaction was applied to the synthesis of fluorinated and deuterated derivatives of the drug phenytoin, of value in drug metabolism and pharmacokinetics studies, producing these derivatives with excellent yields and stereoselectivities.

Conflicts of interest

There are no conflicts to declare

Acknowledgements

We acknowledge the support of Syngenta and the EPSRC (studentship to JMR) and the Schlumberger Foundation (Faculty for the Future Fellowship to MO). We thank Dr Fernando Fernández-Nieto for discussions regarding the selection of the chiral auxiliary, and Prof Craig Butts for assistance quantifying the dr of 9e.

Notes and references


This journal is © The Royal Society of Chemistry 20xx

J. Name., 2013, 00, 1-3 | 3
One sentence summary:
A ‘non-classical’ diastereoselective intramolecular SNAr reaction allows the construction of chiral diarylglycine derivatives in the form of hydantoins related to phenytoin.

Graphical abstract:

```
\begin{center}
\includegraphics[width=0.8\textwidth]{graphical_abstract.png}
\end{center}
```