CHELATION CONTROLLED NUCLEOPHILIC ADDITION OF TETRONIC ACID DIANION TO ALDIMINES: TOWARDS THE STEREOSELECTIVE CONSTRUCTION OF β-AMINO ALCOHOLS

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Abstract---Nucleophilic addition reaction of tetronic acid dianion, derived from tetronic acid with lithium disopropylamide, to aldimines was found to proceed in a stereoselective manner providing syn adducts predominantly via the six-membered chelation transition states.

Development of new methods and strategies for stereoselective carbon-carbon bond formation reactions has intensively been investigated during the last two decades where addition reactions of organometallic compounds or enolates to carbonyl compounds provoked an extraordinary amount of activity by synthetic organic chemist. Chelation control in such addition reactions has well been recognized to play an important role to control the stereochemistry of the newly generated stereogenic centers. We have recently reported the chelation controlled stereoselective addition reaction of tetronic acid or its derivatives, four carbon synthons bearing three oxygen functions, to carbonyl compounds and its application to the synthesis of pentoses, (+)-arabitol and (+)-ribitol. As part of our ongoing effort directed at the utilization of tetronic acid in natural product synthesis, we have further investigated the stereoselectivity of the addition reaction of tetronic acid to aldimines, since such reaction would emerge as a useful implement for the synthesis of β-amino alcohols and other nitrogen-containing natural products.

Thus, the reaction of tetronic acid dianion, derived from tetronic acid and 2.2 equimolar amounts of lithium diisopropylamide (LDA), with benzylideneaniline was carried out at -78 °C in dry tetrahydrofuran under an argon atmosphere and the reaction mixture was quenched by addition of chloromethyl methyl ether to give the syn and anti addition products in 45.9% yield in a ratio of 5.4 : 1. The stereostructure of the major isomer was unambiguously determined to be syn by X-ray analysis as shown in Figure 1.

The stereoselectivity exhibited in the formation of the syn adduct predominantly can be rationalized by assuming that this addition proceeded via a six-membered chelation transition state (A) as depicted in Figure 2 where the arylidene or alkylidene substituent (R1) occupies axial position because the trans geometry of aldimines forces the
metal coordination to nitrogen atom syn to the substituent (R²). Therefore, one of the possible transition states (C) leading to the anti adduct might be excluded in this reaction. In assessing the contribution of the two transition structures having equatorial tetronic acid oxygen to the above consideration, the boat-like transition state (B) seems unfavorable relative to the chair-like transition state (A) because of the usual unfavorable interaction associated

![Figure 1](image)

Figure 1. The ORTEP drawing of the syn adduct.

with the former conformation. When this addition was carried out in the presence of hexamethylphosphoric triamide (20% v/v in THF) as a co-solvent, the conversion yield was increased to 68.7% with slightly decreased stereoselectivity.

*p*-Anisidine was found to be superior to aniline as an amine moiety in terms of conversion yield and stereoselectivity and the results for the other addition reactions were summarized in Table. Although it has been generally recognized that the addition reaction of lithium enolates or organolithium compounds to imines resulted

![Figure 2](image)

Figure 2.

in low yields with the complicated mixture, the reactions of alkylidene-*p*-anisidines with lithium enolate of tetrionic acid afforded the addition products in good yields with high stereoselectivities. The major compound obtained above was stereoselectively converted to an amino alcohol as follows.
Catalytic reduction of 1 over 10% rhodium on alumina in ethyl acetate under 7 atm of hydrogen gave the γ-lactone (2), in 75.8% yield, which on further reduction with lithium aluminum hydride provided the syn amino diol (3) in 96.3% yield.

We are currently exploring this strategy to the synthesis of naturally occurring amino alcohols.

**Table** Nucleophilic Addition Reaction of Tetronic Acid Dianion to Imines

<table>
<thead>
<tr>
<th>R¹CH=NR²</th>
<th>Solvent</th>
<th>Syn : Anti</th>
<th>Yield (%) c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>Ph</td>
<td>THF</td>
<td>5.4 : 1 a)</td>
</tr>
<tr>
<td>Ph</td>
<td>Ph</td>
<td>THF-HMPA</td>
<td>2.1 : 1 a)</td>
</tr>
<tr>
<td>Ph</td>
<td>p-MeOPh</td>
<td>THF-HMPA</td>
<td>3.9 : 1 b)</td>
</tr>
<tr>
<td>Ph</td>
<td>p-MeOPh</td>
<td>THF-HMPA</td>
<td>4.3 : 1 b)</td>
</tr>
<tr>
<td>Ph</td>
<td>p-MeOPh</td>
<td>THF-HMPA</td>
<td>1.3 : 1 b)</td>
</tr>
<tr>
<td>Ph</td>
<td>p-MeOPh</td>
<td>THF-HMPA</td>
<td>73.5 : 1 b)</td>
</tr>
<tr>
<td>2-Phenyl</td>
<td>p-MeOPh</td>
<td>THF-HMPA</td>
<td>11.2 : 1 a)</td>
</tr>
<tr>
<td>Crotyl</td>
<td>p-MeOPh</td>
<td>THF-HMPA</td>
<td>2.0 : 1 a)</td>
</tr>
<tr>
<td>n-Propyl</td>
<td>p-MeOPh</td>
<td>THF-HMPA</td>
<td>&gt;99 : 1 a)</td>
</tr>
</tbody>
</table>

a) The ratio was determined based on the nmr spectrum of the mixture.
b) The ratio was determined by isolated yields of each isomers.
c) Total isolated yield.
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\[ \text{PMP} = p\text{-Methoxyphenyl} \]

Scheme 1.

REFERENCES


7. All the measurements were performed on a Rigaku AFC-5 diffractometer using Cu-Kα radiation. The unit cell dimensions were determined by least-squares calculation from 20 high-angle reflections. Intensity data were collected by using the 2θ/θ scan technique for 6 < 2θ < 110° with an average scan rate of 3°/min. In total 2410 independent reflections were collected, and 1996 satisfying the condition Fo < 3σ(F) were used for calculation. Crystal data for: C_{19}H_{19}N_{4}O_{4}, M_r=325.36. Monoclinic a=11.349(9), b=10.563(5), c=16.940(1)Å, α=90°, β=90°, γ=90°, V=1724(2)Å³, Z=4. Space group P2_{1}/c. The structure was solved by the direct method using MULTAN 80 and the Rigaku crystallographic package RASA-II. The structure was refined by the block-diagonal least-squares method anisotropic thermal parameters for all non-hydrogen atoms. The R factor was finally reduced to 0.102.


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