Amphoteric Molecules
< Chemistry of Andrei K. Yudin >

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Amphoteric molecules

• Amphoteric?
  – Greek word “amphoteros” (both of two)
  – Amphotericism in acid/base chemistry
  – Amino acids (thermodynamic amphotericism)

• Amphoteric molecules
  – Contains functional groups that are normally incompatible
  – Yudin and coworkers
  – Nucleophile & electrophile in one molecule
  – Aziridine aldehydes
  – α-Boryl aldehydes

Other “Amphoteric” molecules

• “Ambiphilic”
  – P. R. Hanson & coworkers
  – [4+4] cyclization of benzosulfonamide with α-quinone methide

• “Amphiphilic”
  – Y. Yamamoto & coworkers
  – Pd-catalyzed allylation reactions

Outline

- Aziridine aldehydes
  - [1,3] Amphoteric system
    - Preparation of aziridine aldehydes
    - Reactions on the aldehyde
    - Reactions on both moieties

- \(\alpha\)-Boryl aldehydes/carboxylic acids
  - [1,2] Amphoteric system

- \(\alpha\)-Boryl cyanate/cyanides
  - [1,3] Amphoteric system

- Acylboronates
  - [1,1] Amphoteric system
[1,3] Amphoteric System: Aziridine Aldehydes

- Orthogonal functional groups
  - Nucleophile: amine (aziridine)
  - Electrophile: aldehyde

- Stability of \(\alpha\)-Amino Aldehyde System
  - Energetically uphill to aziridinium ion
  - Spontaneous Dimerization
  - Fuzed ring of aziridine and 5-oxazolidinol
  - Single diastereomer (X-ray structure)

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• Synthetic Routes
  – From Boc-amino acids
    \[
    \begin{align*}
    \text{NHBoc} & \rightarrow \text{Boc} \\
    \text{R-CO}_2\text{H} & \rightarrow \text{R-C}=(\text{N})=\text{O} \\
    \text{1. isobutyl chloroformate} & \rightarrow \text{N-methyl morpholine} \\
    \text{2. NaBH}_4 & \\
    \text{3. TsCl, KOH} & \\
    \end{align*}
    \]
  – From Serine ester
    \[
    \begin{align*}
    \text{HO-CO}_2\text{R}’ & \rightarrow \text{aziridine ester} \\
    \text{NH}_2 & \rightarrow \text{PPh}_3, \text{DIAD} \\
    \text{aziridine aldehyde} & \rightarrow \text{DIBAL} \\
    \text{Staudinger reaction} & \\
    \text{PPh}_3 & \\
    \text{monomer} & \\
    \end{align*}
    \]
  – From Oxiranyl ester
    \[
    \begin{align*}
    \text{R-CO}_2\text{R}’ & \rightarrow \text{aziridine aldehyde} \\
    \text{O} & \rightarrow \text{NaN}_3 \\
    \text{OH} & \\
    \end{align*}
    \]
Reactions of Aldehydes

- Reduction / Reductive Amination
  - Quantitative yields with borohydride reagents
  - Proceeds via an open-dimer intermediate
  - Release of monomer / fast redimerization

Reactions of Aldehydes

- Peptidomimetic Conjugates
  - Preparation of diamine derivatives

- No epimerization or overalkylation observed
- Attributed to the short lifetime of the open-dimeric imine intermediate (ODI)
- Steric hindrance and low concentration of the ODI prevents overalkylation

Reactions of Aldehydes

- Borono-Mannich Reaction
  - Vicinal aziridine-containing vinyl diamine
    - Exclusively syn selective process
    - Involvement of open-dimeric iminium N,O-chelate
    - Alkenyl group migration onto the si face

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Reactions of Aldehydes

- **Indium (0)-Mediated Diastereoselective Allylation**
  - Organized transition structure accounts for the high diastereoselectivity
  - DFT analysis shows a pocket for Indium surrounded with one N and two O

- **Wittig Reactions**
  - C-vinyl aziridines
  - E/Z controlled by solvent

Reactions of Aldehydes

- Seyferth-Gilbert Homologation
  - Bestmann-Ohira reagent
  - C-ethynyl aziridines (strained propargyl amines)
  - α-amino allene formation with 9-BBN

\[ \text{[Seyferth-Gilbert Homologation diagram]} \]

\[ \text{[Seyferth-Gilbert Homologation reaction]} \]

Reactions of Aziridines (Group Question)

• Initial Interaction of Aldehydes
• Pictet-Spengler Reaction
  – Access to pentacyclic scaffold through a single cascade reaction

\[
\text{Ph} - \text{NH}_2 \xrightarrow{\text{TFE or toluene}} \text{Ph} - \text{NH} - \text{Ph} + \text{Ph} - \text{NH} - \text{Ph}
\]

– Provide the mechanism for the above reaction

\[
toluene \text{ 80 } ^\circ \text{C, mixture of I : II = 1 : 2}
\text{TFE -20 } ^\circ \text{C, exclusively I (>20:1)}
\]

Reactions of Aziridines

- Initial Interaction of Aldehydes
- Pictet-Spengler Reaction
  - Access to pentacyclic scaffold through a single cascade reaction

- Iminium ion formation
- Intramolecular $\text{Ad}_{E}\text{Ar}$ followed by intramolecular aziridine attack
- Solvent and $T$ dependent on diastereoselectivity

Reactions of Aziridines

- Ugi Multi-component Reaction
  - Macrocyclic peptide formation
  - High concentration
  - High diastereoselectivity
  - No epimerization, no dimer/oligomerization observed

![Chemical structures and mechanisms](image)

Reactions of Aziridines

• Mechanism for the Ugi Multi-component Reaction

- Iminium formation
- Isocyanide α-addition
- Transannular attack of aziridine
- Presence of the nucleophilic aziridine at the α-position is responsible for the high yields and high diastereoselectivities

Reactions of Aziridines

- Initial Interaction of Aziridines
- Reaction with Isocyanates

- Solvent dependent (Et$_2$O/HFIP)
- In Et$_2$O: Dimeric carbamate
- In HFIP: Reduced fused hydantoin
- Dimer dissociation under HFIP
- Hydantoin formed when isolated dimeric carbamate product is treated with HFIP

Reactions of Aziridines

- Baylis-Hillman Products
  - Exclusive diastereoselectivity
  - Formation of 8-membered cyclic intermediate (dimeric intermediate)
  - Ring opening by elimination of aziridine

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  – [1,3] Amphoteric system

• Acylboronates
  – [1,1] Amphoteric system
[1,2] Amphoteric System: α-Boryl Aldehydes & Carboxylic Acids

- MIDA (N-methyliminodiacetyl) Boronates
  - Electron-rich boron centers
  - Thermodynamically and kinetically stable C-bound isomer

- Preparation
  - Bench stable white solids
  - IR stretch: 1701 cm\(^{-1}\), \(^1\)H NMR: 9.73 ppm
  - Rearrangement of oxiranyl MIDA boronates
  - 1,2-boryl migration (deuterium labeling)

\[ \text{R} \quad \text{BF}_3 \cdot \text{Et}_2 \text{O} \quad \text{DCM} \quad \text{MeN} \quad \text{B} \quad \text{O} \quad \text{R} \quad \text{H} \]

\[ \text{3a (R} = \text{Ph)} \quad \text{BF}_3 \cdot \text{Et}_2 \text{O} \quad \text{DCM} \quad -30 \text{ to } 0 \degree \text{C} \quad \text{MeN} \quad \text{B} \quad \text{O} \quad \text{R} \quad \text{H} \quad \text{D} \]

\[ 1,2\text{-boryl migration} \]

\[ 4a (98\%) \]

**α-Boryl Aldehyde**

- Various Transformations of the Aldehyde
  - Reaction with amines and amides
  - α-Bromination
  - Pinnick oxidation
  - In-mediated allylation
  - Wittig reaction
  - *gem*-Dibromoalkene
  - Triflate enol ether
  - Silyl enol ether
  - Pd-catalyzed α-allylation

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α-Boryl Aldehyde

- Reactions of the Boronate
- Petasis Reaction
  - C-C Bond formation
  - Via pinacolyl boronate intermediate

- Allylated α-Boryl Alcohol
  - Oxidation with basic peroxide
  - Skipped diene preparation
α-Boryl Aldehyde

- Reactions of the Aldehyde
- Pinnick Oxidation
  - α-Boryl Carboxylic Acids
  - Bench stable white solids

- Configurational stability at α-position of the acid product
- Treatment with t-BuOH/D$_2$O, 0% of deuterium incorporation

\( \alpha \)-Boryl Carboxylic Acid

- Curtius Rearrangement
  - Treatment with DPPA
  - \( \alpha \)-boryl isocyanate ([1,3] system)
  - Bench stable white solids

- Barton Radical Decarboxylative Hydroxylation
  - \( \alpha \)-hydroboronate formation via thiohydroxamate ester
  - Subsequent oxidation to acylboronates ([1,1] system)
[1,3] Amphoteric System:
\( \alpha \)-Boryl Isocyanates

- \( \alpha \)-Boryl isocyanate
  - Ureas
  - Manipulation of MIDA group to boronic acid derivatives
  - Carbamates
  - Boropeptides
Combined $[1,3]/[1,1]$ Amphoteric System: $\alpha$-Boryl Isocyanides

- $\alpha$-Boryl Isocyanide
  - HSiCl$_3$ mediated deoxygenation
  - Combination of two amphoteric systems: $[1,3]$ & $[1,1]$ system

- Other Reactivities
  - Sulfurization to isothiocyanates
  - Reaction with amines (thiourea)
  - Tetrazole formation
Combined [1,3]/[1,1] Amphoteric System: \(\alpha\)-Boryl Isocyanides

- Multicomponent reaction (U4CR/P3CR)
  - Ugi reaction
  - Passerini reaction
  - These borocyclic peptide derivative exhibit comparable results and selectivities to bortezomib

[1,1] Amphoteric System: Acylboronates

• Thiazole Synthesis
  – \( \alpha \)-Bromination followed by reaction with thioamides/thioureas
  – Carbon-Boron bond intact

\[
\begin{align*}
\text{MeN} & \quad \text{Br}_2 \\
\text{R}^1 & \quad \text{dioxane/DCM (1:1 v/v)}
\end{align*}
\]

\[
\begin{align*}
\text{MeN} & \quad \text{Br} \\
\text{R}^1 & \quad \text{DMF}
\end{align*}
\]

• Quinoxaline Synthesis
  – Silyl enol ether formation
  – Rubottom oxidation
  – \( \alpha \)-borylated diketones
  – Subsequent DM oxidation

Summary

• The syntheses of compounds with [1,3]-, [1,2]-, and [1,1]-amphoteric systems and its synthetic utility in various reactions have been studied by Yudin and coworkers.

• Amphoteric compounds:
  – are mostly bench stable solids
  – show orthogonality of nucleophilic and electrophilic components.

• Aziridine aldehydes:
  – exists in dimers via self-association
  – benefit high stereoselectivity from having dimeric nature

• α-Boryl aldehydes:
  – Isolable amphoteric metalloids
  – Retention of the C-B bond
Useful References