Continuous anodic oxidation of TEMPO as a mediator for selective synthesis of aldehydes from primary alcohols

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Outline

• Anelli Oxidation
• One-Phase Approach
  • Mixing and Residence Time
• Multi-Phase Approach
  • Mixed Double Emulsions
• Electrooxidation
  • Voltammetry Experiments → Batch Process → Continuous Process
• Outlook

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Anelli Oxidation


Pre-oxidation of TEMPO

- NaOCl in situ causes *side products*
- Br$_2$ in organic solvents (*requires separation*)
- electrochemical oxidation in water (*several alcohols insoluble, solvent changes, phase separation*)

multiphase flow with excess of TEMPO+
One-Phase Approach

Small window for efficient mixing; broad residence time distribution

Mixing controlled; broad residence time distribution

Residence time controlled

Mixing and residence time controlled
One-Phase Approach

Residence time $t_R = \frac{\text{Channel length}}{\text{Volume flow}}$

- **Constant volume flow; different capillary length**
  - $t_R = f(\text{capillary length})$
  - Constant mixing efficiency

- **Constant capillary length; different volume flow**
  - $t_R = f(\text{volume flow})$
  - Programmable mixing efficiency

Measurable
One-Phase Approach

Residence time dependency:

- Fixed flow rates
- Observation by GC and by eye (bleaching)
- Full conversion after approx. 3.5 min
- No significant differences between mixer types and flow patterns
  - Kinetic limit reached
One-Phase Approach

Flow rate/mixing dependency:
- Fixed reactor volume
- Conversion decreases with increasing residence time
  - Decreasing flow rate/mixing efficiency
- Increased reaction time unable to compensate loss in mixing efficiency

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Multi-Phase Approach

Coaxial double emulsion generator
- 2 T-junctions to insert core and shell capillary into main channel
- Coplanar outlet of inner capillaries
- Core droplet is infused into shell droplet while latter is generated


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Multi-Phase Approach

Passive mixing:
- Gravity induced
- Capillary coiled on cylinder
- Double emulsion, core droplet pulled downwards by gravity
  - Crosses shell droplet twice every winding


Video: [Link]
Multi-Phase Approach

Gravity induced mixing:

- Oxidant and alcohol in different phases
  - Interface reaction
  - Extended reaction time necessary
- 9-fold excess of TEMPO+ reduces reaction time to 17 min
- Easy recycling of remaining TEMPO+
Multi-Phase Approach

Active mixing:
- Retention unit mounted on orbital shaker
- Double emulsion, jiggling of core droplet
  - Stirring of shell phase with adjustable frequency

Video: Link

Multi-Phase Approach

Stirred double emulsion:
- 1.7 eq of TEMPO+ used
- Conversion 12% in 3 min without mixing
- Increase to approx. 22% conversion between 0.2 Hz and 0.5 Hz
- Maximum expected around 0.35 Hz
- Further Investigation necessary
Electrooxidation

Disproportionation of TEMPO:
- Full conversion to TEMPO+ and TEMPOH at pH = 0
- At pH = 2 TEMPO+ yield is 68%  
  - Proportion of 33% of TEMPO+, TEMPO and TEMPOH each
- pH ≥ 3 suppresses disproportionation

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Electrooxidation

**Comproportionation of TEMPO⁺ and TEMPOH:**
- **TEMPOH** formed in situ by adding 1 to **TEMPO⁺**
- Almost total comproportionation at pH = 9
- 80% **TEMPO⁺** left in neutral media
- No comproportionation at pH = 2

**Alcohol oxidation with stochiometric amounts of TEMPO⁺ requires pH < 2**
Electrooxidation

CV and RDE measurements of TEMPOH:
- No conversion to TEMPO+ observed in acidic medium (pH = 2)
- Neutral or alkaline medium required
- Intermediary TEMPO not observed
  - Proved by additional CV/RDE measurements of TEMPO
Electrooxidation

Oxidation path:
- Easy oxidation $\text{TEMPO} \rightarrow \text{TEMPO}^+$
- No direct oxidation $\text{TEMPOH} \rightarrow \text{TEMPO}^+$
- Only in alkaline media
  - Preceding deprotonation to $\text{TEMPO}^-$
  - $\text{TEMPO}^- \rightarrow \text{TEMPO} \rightarrow \text{TEMPO}^+$
  - $\text{TEMPO}^- \rightarrow \text{TEMPO}$ much slower than $\text{TEMPO} \rightarrow \text{TEMPO}^+$

Electrooxidation

Batch electrolysis:
- Maximum yield 33%
- Decomposition of water acidifies anolyte
  - Disproportionation of TEMPO
Electrooxidation

Batch electrolysis:
- Maximum yield 33%
- Decomposition of water acidifies anolyte
  - Disproportionation of TEMPO
- TEMPOH associates with TEMPO
  - Oxidation is prevented


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Electrooxidation

Catholyte in
0.1M Na$_2$SO$_4$

Anolyte out

Catholyte out

Anolyte in
0.1M Na$_2$SO$_4$
0.1M TEMPOH
pH 8

Catholyte in

Catholyte out

Anolyte in

Anolyte out
Electrooxidation

Continuous electrolysis:
- Decomposition of water $\rightarrow$ acidification
- Maximum yield 33%
- Buffering at pH = 7 prevents dimerization, lowers oxidation yield due to protonation of TEMPO-

Graph showing the concentration of TEMPO+ and TEMPO under different conditions:
(a) $U = 1.5\ V;\ pH = 8$
(b) $U = 2.0\ V;\ pH = 8$
(c) $U = 2.0\ V;\ pH = 7$, buffered

TEMPO chemical structure:
- $2 e^-$
- $+ H^+$
- Electrolysis

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Outlook

Electrochemical microstructured reactor:

- Divided cell (Nafion™ membrane)
- Ti meshed metal baffle, platinized
- Galvanostatic mode

Challenges:

- pH change required
- Flow rate adjustment
- Continuous phase separation
- Recirculation of mediator

Objective: Fully automated process

Outlook

API synthesis from natural/renewable resources
• Antitumor and –inflammatory properties
• Treatment of leukemia, malaria etc.

Betulin (3β)-Lup-20(29)-en-3,28-diol

Selective Oxidation
CrO₃

Betulin aldehyde

Betulnic acid and derivates

Betula pendule
Fraxinus americana
Sorbus americana

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Conclusions

• One-phase process requires much shorter reaction time than multi-phase reaction
• Multi-phase approach simplifies oxidans recycling significantly
  • Allows usage of huge excess of oxidans
  • Allows mixing in segmented flow
• Disproportionation equilibrium of TEMPO requires pH < 2 for optimal oxidation conditions
• Alkaline medium required for reoxidation of TEMPOH
• Water decomposition and association of TEMPOH and TEMPO major problems in batch and continuous oxidation, maximum yield of TEMPO+ 33%
• Fully integrated continuous process requires pH changes and continuous phase separation
• Applications in API synthesis, focus on betulin and derivates
Thank You!

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