- First described by Meisenheimer (1926)
- Commercialized in 1954
- Abbreviation: PNO
- > 19,000 (1 step) reactions on Scifinder, not including patents
- Many drugs contain N-oxides
- Standard aromatic reactions (like Sandmeyer etc.) are not covered. Radical reactions also not covered, except for 1 example (full coverage would be a separate group meeting).

Differences to pyridine
- PNO is more nucleophilic
- PNO is more electrophilic
- Higher dipole-moment [4.37 D (PNO) vs 2.03 D (pyridine)]
- Much weaker base [pKa = 0.79 (PNO) vs pKa = 5.2 (pyridine)]

Mesomeric forms

- Preferred attack of both electrophiles and nucleophiles at either oxygen, the 2- or the 4-position
- O-protonated species reacts like deactivated pyridine
- Reactions involving nucleophilic aromatic substitutions (SNAr) are comparable (but faster) to the once of pyridine and are not covered in this group meeting.
Pyridine N-Oxides

Multiple oxidations can be tricky...

1. Pyridine N-oxide
   - mCPBA (1.0 eq) in CH$_2$Cl$_2$, r.t., 13 h, 40% yield
   - mCPBA (3.5 eq) in CH$_2$Cl$_2$, r.t., 13 h, 83% yield
   - AcOH, aq. H$_2$O$_2$ at 90 °C, 18 h, 73% yield


... or almost impossible

1. Pyridine N-oxide
   - AcOH, aq. H$_2$O$_2$ at 70-75 °C, 3 h, 70-80% yield
   - HOF-CH$_3$CN ($F_2$+H$_2$O+CH$_3$CN) at 0 °C, 5 min, > 60% yield

2. Maerker, Case JACS 1958, 80, 2745.

De-novo syntheses

1. CuBr(Ph$_3$P)$_3$ (10 mol%) + Ph$_3$P (10 mol%) in DMSO at 120 °C, 71% yield

2. MeO- + CH$_2$C- + N- + Me
   - 1) Na$_2$CO$_3$
   - 2) ROH-HCl via

Just for fun

2. Davies, Marcoux, OL 2001, 3, 209-211.
**Pyridine N-Oxides**

*via* condensation reactions


*via* rearrangements/cycloadditions


Deoxygenation without further functionalizations

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349-351. (see also for references on deoxygenations)
Pyridine N-Oxides

Nucleophilic reactions on PNO
In general, the oxygen atom attacks an electrophile followed by a subsequent 1,2- vs 1,4-addition of a nucleophile displacing the O-LG moiety. Additionally, SNAr can take place (not covered).

Chlorinations

\[
\begin{align*}
\text{Pyridine N-Oxide} & \xrightarrow{\text{POCl}_3, \text{neat, 110 °C, 2 h}} [\text{Pyridine N-Oxide} + \text{Pyridine}]
\end{align*}
\]

<table>
<thead>
<tr>
<th>Compound</th>
<th>Yield</th>
<th>Isomer A</th>
<th>Isomer B</th>
<th>Isomer C</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-CN</td>
<td>83%</td>
<td>88:10:2</td>
<td>93%</td>
<td>80:20:0</td>
</tr>
<tr>
<td>R-CONMe₂</td>
<td>74%</td>
<td>47:38:15</td>
<td>82%</td>
<td>70:30</td>
</tr>
<tr>
<td>R-Cl</td>
<td>82%</td>
<td>32:46:22</td>
<td>84%</td>
<td>34:47:19</td>
</tr>
<tr>
<td>R-Ph</td>
<td>80%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R-NMe₂</td>
<td>81%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Ratio given as A:B:C


Brominations only rarely used

<table>
<thead>
<tr>
<th>Compound</th>
<th>Yield</th>
<th>Isomer A</th>
<th>Isomer B</th>
<th>Isomer C</th>
</tr>
</thead>
<tbody>
<tr>
<td>X-CO₂Me</td>
<td>84%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>X-OBn</td>
<td>92%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>X-Br</td>
<td>88%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>X-NH₂</td>
<td>90%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Brominations usually done with Br₂ in CCl₄. However, selectivities are moderate and highly dependent on substituents:


Aminations – not this way...

Keith, JOC 2006, 71, 9540-9543.

...but this way!

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Fluorinations and iodinations usually done by SNAr.
Pyridine N-Oxides

The scope of this reaction was further broadened:

Using PyBrop


**Pyridine N-Oxides**

**Sulfurylations**

\[
\begin{align*}
\text{O} & \quad \text{Ad} = \text{Adamantyl} \\
\text{HSA\text{Ad}} & \quad \text{Ac}_2\text{O} \quad \text{reflux} \\
\end{align*}
\]

**Phosphorylation**

\[
\begin{align*}
\text{O} & \quad \text{Me}_2\text{SO}_4 \quad 67\% \\
\text{O} & \quad \text{NaP}_2\text{O}\text{Et} \quad \text{OEt} \\
\end{align*}
\]


**Oxidation**


**Cyanation**

\[
\begin{align*}
\text{N} & \quad \text{Ac}_2\text{O} \quad \text{reflux} \\
1) \text{AcCl} & \quad 81\% \\
2) \text{KCN} & \quad \text{Me}_2\text{SO}_4 \quad \text{(neat)} \\
\end{align*}
\]

Feely, *JACS* 1959, 81, 4004.

Rationale for 3-substituted products

\[
\begin{align*}
\text{N} & \quad \text{SAd} \quad \text{Ad} \quad \text{Me} \\
\text{O} & \quad \text{O} & \quad \text{O} & \quad \text{O} \\
\text{H} & \quad \text{H} & \quad \text{H} & \quad \text{H} \\
\end{align*}
\]

**Comprehensive review:** Bauer, *Heterocycles* 1986, 24, 161-179.

**Reissert reaction**

\[
\begin{align*}
\text{Me}_2\text{NCOCl} (1.0 \text{ eq}) & \quad \text{Me}_3\text{SiCN} (1.1 \text{ eq}) \\
\text{CH}_2\text{Cl}_2 \quad \text{r.t., 1-5 d} & \quad \text{MeCN} \quad 110 \degree \text{C}, 12 \text{ h} \\
\end{align*}
\]


**Modified Reissert reaction**

\[
\begin{align*}
\text{Me}_3\text{SiCN} (2.5 \text{ eq}) \\
\end{align*}
\]

**Vorbr.** 80%, 41%, 80% (50:50), 89%, 73%, 76%
Pyridine N-Oxides

Andreas Weickgenannt

Alkylations, Alkenylations, Arylations, Alkynylations

1) PhMgBr
2) H₂O

not directly

Ac₂O, reflux

Ac₂O, reflux

fast and disrotatory

Mechanistic understanding: Kellogg, JOC 1971, 36, 1705-1708.

2.5 kg scale
80%
p38 MAP kinase inhibitor
(treatment of rheumatoid arthritis and psoriasis)

Pyridine N-Oxides

Andreas Weickgenannt

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Radical reactions and photochemistry (separate GM necessary)


Summary:
Pyridine N-Oxides

**Electrophilic substitutions**

- **Br** (2 eq) + Ti(OAc)$_3$ (3 eq) + AcOH, 70 °C, 24 h: 53%
- **Br$_2$** (2 eq) + Ti(OAc)$_3$ (3 eq) + AcOH, 70 °C: 70%
- **H$_2$SO$_4$** + HgSO$_4$, 240°C: 49%
- **H$_2$SO$_4$** + HNO$_3$, 80-90 °C: 80-90%

**Coordination helps:**

- **Et$_3$OBF$_4$** with CHCl$_3$ reflux: 80%
- **N$_2$O$_4$** with CHCl$_3$ reflux: 80%

The use of LiTMP gives much worse results.

**Metallations**

- **nBuLi** + ketone, Et$_2$O, -65 °C: 77%
- **nBuLi** + ketone, THF, -78 °C: 67%
- **nBuMgCl** or **iPrMgCl** (1.7 eq), THF, -78 °C: 90%

The breakthrough: Using RMgBr instead of nBuLi as the base.

For related reactions using bromine/iodine-magnesium exchange, see:
- **Quéguiner, Tetr. Lett. 2008, 49, 6901-6903.**
- **Abramovitch, JOC 1972, 37, 1690-1696.**
- **Almqvist, Tetrahedron Lett. 2008, 49, 6901-6903.**

(a) **Quéguiner, Tetr. Lett. 2000, 56, 1349-1360; b) Duan, JOC 2009, 74, 939-942.**
Pyridine N-Oxides

Cycloadditions

[1] Larock, JOC 2006, 71, 4689-4691. The first intermediate can also be accessed by treating PNO with Ar_3^+BF_4^- resulting in an O-arylation with subsequent addition onto the pyridine: Abramovitch, Tetrahedron Lett. 1977, 1109-1112.


Pyridine N-Oxides

Functionalizations of the side-chain with participation of PNO

Just one rearrangement:

\[
\text{Pyridine} \rightarrow \text{Pyridine}
\]


Drugs containing PNO's

Dr Proctor's Hair Regrowth Shampoo

JPL-153 (anti-HIV)

Functionalizations of the side-chain with participation of PNO

Drugs containing PNO's


<table>
<thead>
<tr>
<th>Structure</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>![Structure1]</td>
<td>cytotoxic pro-drug</td>
</tr>
<tr>
<td>![Structure2]</td>
<td>CCR5 antagonist</td>
</tr>
<tr>
<td>![Structure3]</td>
<td>P1 N-benzylamide thrombin inhibitor</td>
</tr>
<tr>
<td>![Structure4]</td>
<td>natural product</td>
</tr>
</tbody>
</table>

Drugs containing PNO's

- Dr Proctor's Hair Regrowth Shampoo
- JPL-153 (anti-HIV)

Additional uses of PNO

PNOs can be used as oxidants in a number of transformations. For a brief summary in the introduction, see: Sajiki, Eur. J. Org. Chem. 2011, 3361-3367.
(see also: KCN, PSB, Angew. Chem. Int. Ed. 2002, 41, 993-996)

PNOs can also be used as chiral ligands and organocatalysts:

Very famous is their use as reagents in radical decarboxylations, referred to as the Barton decarboxylation. For a recent review on the applications of this transformation, see: Almeida, Tetrahedron 2009, 65, 3563-3572.

For a related decarboxylation of acid anhydrides yielding aldehydes, see: Rüchardt, Eichler, Krätz, Tetrahedron Lett. 1965, 233-236.

Reviews used for this Group Meeting