Introduction

The Sandmeyer reaction is a chemical reaction used to synthesize aryl halides from aryl diazonium salts. The reaction is a method for substitution of an aromatic amino group via preparation of its diazonium salt followed by its displacement with a nucleophile. The nucleophile in this case is hypophosphorus acid, $\text{H}_3\text{PO}_2$.

Mechanism

The nitrous acid is usually prepared in situ from sodium nitrite and an acid. Following a $2^{\text{nd}}$ protonation step, one equivalent of water is lost to form nitrogen monoxide cation i.e. the “nitrosonium ion” electrophile. An aromatic (or heterocyclic) amine quickly reacts with a nitrite to form an aryl diazonium salt.

\[
\begin{align*}
\text{NaNO}_2 & \xrightarrow{\text{HB}} \text{HO}^-\text{N} = \text{O}^- \xrightarrow{\text{HB}} \text{H}_2\text{O}^-\text{N} = \text{O}^- \xrightarrow{\text{H}_2\text{O}} \text{N} = \text{O}^+ \\
\text{ArNH}_2 & \xrightarrow{\text{NO}} \text{ArN}^+\text{N} = \text{O}^- \xrightarrow{\text{H}_2\text{O}} \text{ArN}_2^+\text{X}^- \xrightarrow{\text{CuX}} \text{ArX}
\end{align*}
\]

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Variations

The majority of variations of the Sandmeyer reactions consist of using various copper salts. For example, using cuprous cyanide produces benzonitriles. Substituting thiols or water for the copper salts generates thioethers or phenols, respectively.

The Schiemann reaction uses tetrafluoroborate and delivers the halide-substituted product, fluorobenzene, which is not obtained by the use of copper fluorides.

Sandmeyer reactions with copper salts used in catalytic amounts are also known. One bromination protocol employs a 0.2 equivalent Cu(I)/Cu(II) mixture with additional amounts of the bidentate ligand phenanthroline and phase-transfer catalyst dibenzo-18-crown-6:

[Diagram of the reaction]
Amyl nitrites are also useful as reagents in a modification of the Sandmeyer reaction. The reaction of the alkyl nitrite with an aromatic amine in a halogenated solvent produces a radicalaromatic species, this then abstracts a halogen atom from the solvent. For the synthesis of aryl iodides diiodomethane is used, whereas bromoform is the solvent of choice for the synthesis of aryl bromides.

### Aliphatic variation

William Reusch at Michigan State University states:

“The distinct behavior of 1°, 2° & 3°-aliphatic amines is an instructive challenge to our understanding of their chemistry, but is of little importance as a synthetic tool. The SN1 product mixtures from 1°-amines are difficult to control, and rearrangement is common when branched primary alkyl groups are involved. The N-nitrosamines formed from 2°-amines are carcinogenic, and are not generally useful as intermediates for subsequent reactions.”

The aliphatic version of the Sandmeyer reaction was used to prepare Batimastat and marimastat though (from 1° amino acids).

### References


15. https://www2.chemistry.msu.edu/facul...jml/amine2.htm

Contributors

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