Cyanogen bromide is a versatile solid reagent which is used widely in organic synthesis and biochemistry. The reagent has many uses in synthetic organic chemistry, such as for the synthesis of guanidines, hydroxyguanidines, heterocyclic systems, ureas and thioureas.\(^1\)

**Cyanogen bromide**

Cyanogen bromide is usually written as CNBr, though this is misleading as the carbon atom has a triple bond to nitrogen and a single bond to bromine (\(\text{N}≡\text{C}-\text{Br}\)). The electronegative bromine and nitrogen atoms shift electron density away from the carbon atom in this linear molecule, making it particularly electrophilic and susceptible to nucleophilic attack.

CNBr is a source of electrophilic cyanide, and reacts with primary and secondary amines to yield cyanamides (1), which can be reacted further with amines or hydroxylamines to yield guanidines (2) and hydroxyguanidines (3) respectively (Scheme 1).

Snider and O’Hare have used this technique to synthesize hindered guanidine 4 as a model for the naturally occurring bradykinin receptor antagonist Martinelic acid.\(^2\) Attempts to form the guanidine directly from a pyrrolidine precursor resulted in poor yields, and the success of the two step process using cyanogen bromide is attributed to the lower steric hindrance (CNBr is a small, linear molecule) and higher electrophilicity than reagents such as N-butyl-N′-Boc-thiourea which can form guanidines directly.

<table>
<thead>
<tr>
<th>Code</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>FC02319</td>
<td>Cyanogen bromide</td>
</tr>
<tr>
<td>FC04239</td>
<td>Cyanogen bromide 30% w/w in acetonitrile</td>
</tr>
<tr>
<td>FC03962</td>
<td>Cyanogen bromide 34% w/w in dichloromethane</td>
</tr>
<tr>
<td>FC07135</td>
<td>Cyanogen bromide 50% w/w in acetonitrile</td>
</tr>
<tr>
<td>FC07908</td>
<td>Cyanogen bromide 50% w/w in toluene</td>
</tr>
</tbody>
</table>

Additional Information

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Cyanogen bromide is a convenient reagent for the synthesis of amino-heterocycles (Scheme 3). For example, amino 1,3,4-oxadiazoles (5) can be readily formed from hydrazide precursors and aminobenzoxazoles (6) and aminobenzimidazoles (7) synthesized by treatment of the o-aminophenol or o-diamine respectively with CNBr.4

\[
\begin{align*}
\text{CNBr, MeOH} & \quad \rightarrow \\
\text{CNBr, MeOH, DCM} & \quad 6, X = O \\
\text{CNBr, MeOH} & \quad 7, X = NH
\end{align*}
\]

Scheme 3

Reaction of a tertiary amine with CNBr results in the formation of a disubstituted cyanamide with the loss of one of the original substituents on nitrogen as an alkyl bromide (the von Braun reaction), as illustrated in Scheme 4 for the synthesis of N-methyl-1-naphthcyanamide.5 The alkyl group that cleaves is usually the one which yields the most reactive alkyl halide,6,7 and the von Braun reaction has also been used to cleave aziridine rings.8

\[
\begin{align*}
\text{CNBr, reflux} & \quad \rightarrow \\
\text{CNBr, reflux} & \quad + \quad \text{MeBr}
\end{align*}
\]

Scheme 4

Von Braun has reported that dialkyl thioethers can be cleaved by CNBr to yield alkyl thiocyanates and an alkyl bromide (Scheme 5).1,9 The reaction has been used to cleave peptides at the C-terminus of methionine residues and has utility in the reduction of polypeptides for identification and sequencing. The nucleophilic sulfur in methionine attacks the electrophilic carbon of cyanogen bromide, but the sulfur in cysteine residues does not react, making the technique selective for cleavage at methionine residues. Cleavage yields are frequently high except where the methionine residue is followed by a serine or threonine residue. In these cases modified buffer conditions have been reported which produce greater yields.10,11

\[
\begin{align*}
\text{CNBr, 60°C} & \quad \rightarrow \\
\text{CNBr, 60°C} & \quad + \quad \text{MeBr}
\end{align*}
\]

Scheme 5

In biochemistry, cyanogen bromide is frequently used to immobilize proteins for affinity chromatography by coupling them to reagents such as agarose (a polymer based on alternating monomers of β-D-galactopyranose and 3,6-anhydro-α-L-galactopyranose). Cyanogen bromide activation is one of the most common methods for preparing affinity gels, and is useful because it reacts with the hydroxyl groups on agarose to form cyanate esters and imidocarbonates, which are attacked by primary or secondary amine nucleophiles from the protein, resulting in immobilization of the protein on the agarose matrix.12,13
Sokolova and colleagues have reported the use of cyanogen bromide as a coupling reagent for the formation of phosphoroamidate or pyrophosphate internucleotide bonds in DNA duplexes.\(^\text{14}\) Compared to alternative reagents such as water-soluble carbodiimide that are often used for this process, CNBr is advantageous as it is highly reactive and yields no modified products.

Biosynth Carbosynth supplies cyanogen bromide in solid form (product code FC02319) and as solutions in CH\(_2\)Cl\(_2\), toluene and acetonitrile (FC03962, FC07908 and FC07135 respectively).

**References**