

Nitrations and other hazardous chemistries

Mastering the challenge of today's pharma needs

Archimica is a leading company for a very broad range of hazardous chemistries for the efficient production of intermediates and APIs. The technology portfolio involves nitrations, alkali metals, cyanide chemistry and many others. These methods are combined with state-of-the-art technologies in organo-metallic, enzymatic and heterocyclic chemistry.

Archimica groups hazardous chemistries into highly exothermic reactions, thermally or mechanically unstable compounds or highly reactive substances. Despite the considerable risks involved in using such reactions or materials on a large scale, their application is justified in many cases in which there are no reasonable alternatives. In some cases such hazardous chemistries significantly reduce the number of chemical steps. In many cases there is

no other way to produce certain molecules except by the reactions possible by using hazardous chemicals.

Through decades of experience in working with hazardous compounds up to very large scale, Archimica maintains the highest level of safety and environmental standards with even the most hazardous and difficult to handle reagents and solvents, both under cGMP and non-GMP conditions.

Hazardous chemistries under cGMP: wherever, whenever you need them

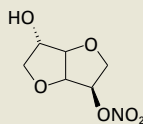
Acetone cyanohydrine	Dimethyl sulfate	Permanganates
Acetylnitrate	Dimethylsulfoxide (DMSO)	Phosphorous oxybromide
Alkyl lithiums	Ethylene oxide	Phosphorous oxychloride
Alkyl magnesium halides	Hydrazine	Propene
Alkyl silanes	Hydrogen	Propoxyethylchloride
Ammonia	Hydrogen cyanide	Reactive chlorides (Thionyl chloride, sulfonyl chloride)
Aryl magnesium halides	Hydrogen peroxide (H ₂ O ₂ , up to 70 %)	Silanes
Benzene	Iodine, methylene diiodide, methyl iodide, iodoform	Sodium borohydride
Bis(2-chloroethyl)amine	Li-Selectride	Sulfides
Bromine, brominating agents	Lithium, magnesium, sodium	Sulfur trioxide, sulfur dioxide
Carbon monoxide (low pressure)	Lithium aluminum hydride	Titanium tetrachloride
Chlorinated solvents	Methoxyethylchloride	Trimethylsulfoxonium iodide (TMSOI)
Chloroform	Nitric acid (fuming)	Thiophenols
Chlorine	Oleum	
Chloroalkylsilanes		
Chlorosulfonic acid		
Cyanides		
Cyclopentadiene		

Nitrations

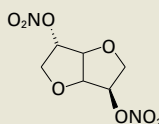
Archimica has been performing nitrations for decades. At our Sandycroft site in the UK, we produce isosorbide mononitrate (ISMN) on a large scale via the reaction of isosorbide with red fuming HNO_3 .

All safety and risk assessment procedures as well as specialised equipment are in place at different Archimica sites to perform nitrations up to very large scale. As one of the very few nitrators left in the Western world, Archimica is a tested and reliable partner for new nitration and nitric acid oxidation projects.

Nitration products



Isosorbide mononitrate (ISMN)



Isosorbide dinitrate (ISDN)

Reactive metals and alkyllithiums

Archimica uses lithium, magnesium and sodium as well as various alkyllithiums in its organometallic technology portfolio. As an example, lithium granules are used in a patented process for deprotonations of benzene and heteroarene rings, offering a much more economic approach for such deprotonations compared to butyllithium. This technology portfolio is backed by

unique equipment in cryogenic reactors from few L up to very large production scale at almost all sites ($-90\text{ }^\circ\text{C}$). To better deal with the severe safety risks posed by the reactions of lithium and other alkali metals, Archimica has invested significant efforts into safety studies. Archimica has now been successfully handling such reactions at large scale for almost a decade.

Cyanides and HCN

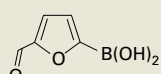
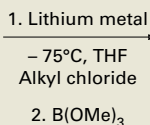
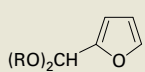
Archimica's technology portfolio involves all kinds of transformations using alkali cyanides and acetone cyanohydrine. Special palladium-based catalysts allow the substitution of aryl halides to aryl nitriles. The enzymatic application portfolio of Archimica involves oxynitrilase handling, yielding enantiopure cyanohydrins, mandelic acids, amino alcohols and other derivatives. In such reactions, it is often a requirement to apply HCN which is generated by in-situ methods to avoid serious safety risks.

Other hazardous chemistries

Over the decades of production experience at Archimica, a broad portfolio of further hazardous chemistries has been developed and scaled. These reactions allow us to offer high efficiencies in terms of time/space yield, productivity and waste generation, quite often synthetic shortcuts, and sometimes access to products which are not available with "classical" chemical methods.

One of the main strengths of the Archimica group is the ability to combine such hazardous reactions with "state-of-the-art technologies" in the highly differentiating fields of modern organometallic, enzymatic and heterocyclic chemistry.

Archimica's lithium technology



General substitution technology for butyllithium

- improved process economy
- high selectivities
- higher yields compared to BuLi (+ 10 %)