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Custom Development & Manufacturing Organization (CDMO)

Chlorosulfonyl Isocyanate (CSI): The Raw Material to Synthesize Carbamates, Lactams, Sulfamides and Many More

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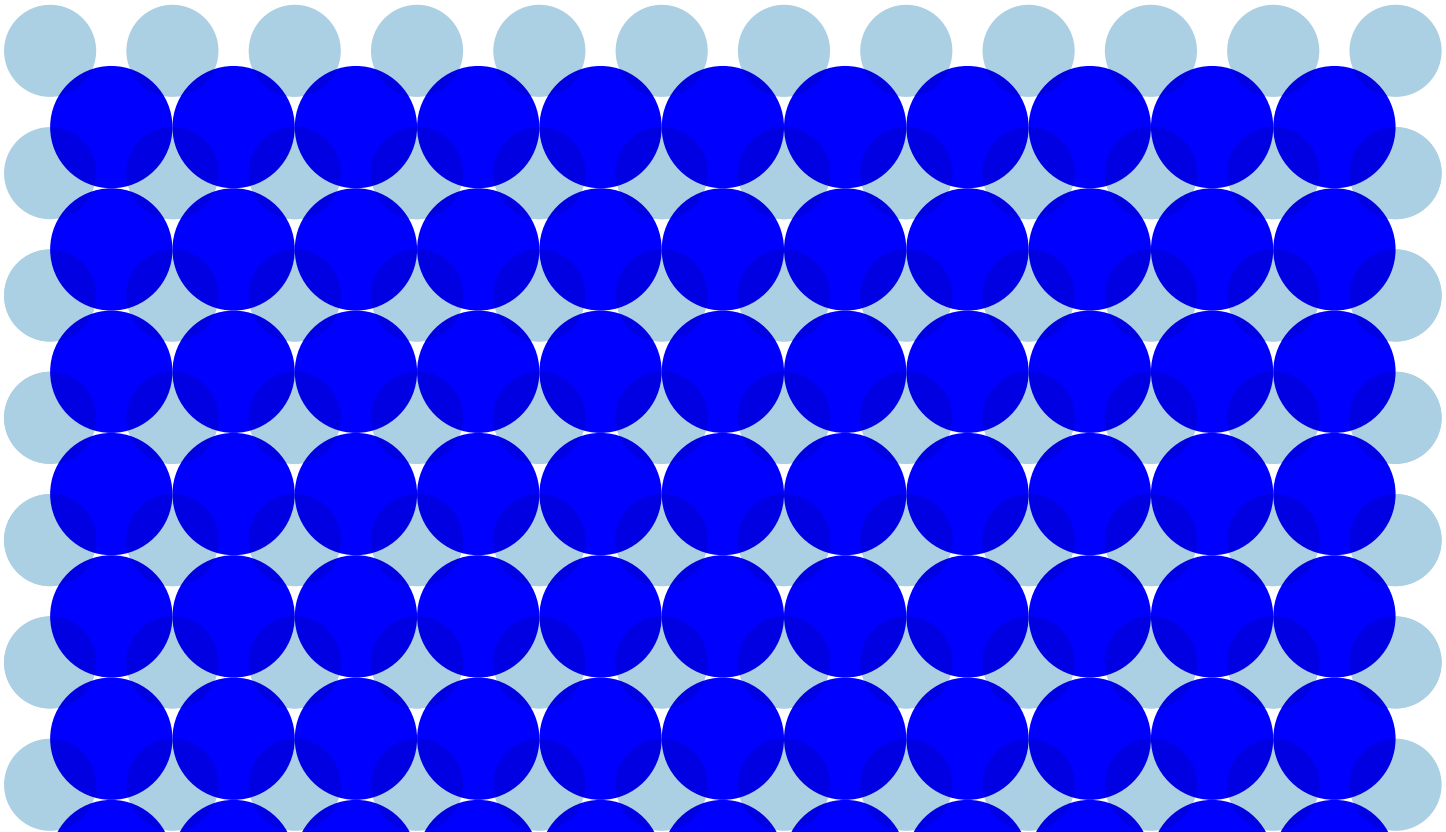
Explore the remarkable versatility of chlorosulfonyl isocyanate (CSI). Discovered in 1956, CSI has become a commonly used compound in organic chemistry, due to its high reactivity. From sulfamoylurea derivatives with antibacterial properties to carbamates essential in industry, CSI's applications are vast. It extends its influence into inorganic chemistry, contributing to lithium-ion battery materials with enhanced performance. Moreover, CSI serves as the foundation for the Burgess reagent, facilitating diverse organic synthesis processes. With its broad utility and practical applications, CSI drives innovation across pharmaceuticals, energy storage, and beyond.



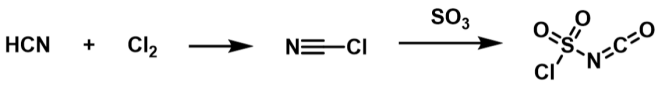
Chlorosulfonyl Isocyanate (CSI): The Raw Material to Synthesize Carbamates, Lactams, Sulfamides and Many More

Have you ever heard of chlorosulfonyl isocyanate (CSI)? CSI reacts with a range of functional groups such as amines, alcohols, olefins, carboxylic acids, and epoxides to form sulfamides, carbamates, lactams, sulfamates and carbonates. CSI is the common choice for the insertion of the sulfamoyl moiety in various organic molecules. In recent years, CSI has also been employed in inorganic chemistry, more precise in an alternative pathway for the preparation of Li-ion battery materials.

Chlorosulfonyl isocyanate (CSI) is one of the most chemically reactive isocyanates known.[1] Since its discovery by Graf in 1956,[2-3] CSI has become a key molecule for the insertion of the sulfamoyl moiety (-SO2NH-) in various compounds. Its remarkable reactivity is mainly due to its strong electrophilicity. There are two sites where nucleophilic attacks can occur: the most reactive one is the carbon of the isocyanate moiety, and the other one is the sulfur atom bound to a strongly electronegative chlorine atom. Therefore, the use of CSI in chemical synthesis requires non-nucleophilic, inert, and anhydrous solvents such as chlorinated solvents, acetonitrile, or toluene.

CSI is commercially available on a large scale and is produced starting from hydrogen sulfur trioxide and cyanogen chloride (Scheme 1) at one of Arxada's dedicated plants in Visp, where we are also able to produce the precursor cyanogen chloride by reacting hydrogen cyanide with chlorine gas.[4-5-6] The process is therefore completely internalized. On top of that, Arxada has decade-long experience of carefully handling the reactivity of the final product, providing safe and adequate packaging, for carrying out shipments to the customers.

Scheme 1. Synthesis of CSI starting from hydrogen cyanide and chlorine.



CSI has been shown to undergo a wide range of reactions with compounds which have various functional groups (Scheme 2).

The reaction with amines gives sulfamoylurea derivatives (**1**), compounds endowed with good antibacterial properties which can also be used as effective agrochemicals.[7-8]

The reaction with alcohols yields carbamates (**2**),[9-10] which have a wide range of applications in organic synthesis, the paint industry, agriculture, and pharma.[11]

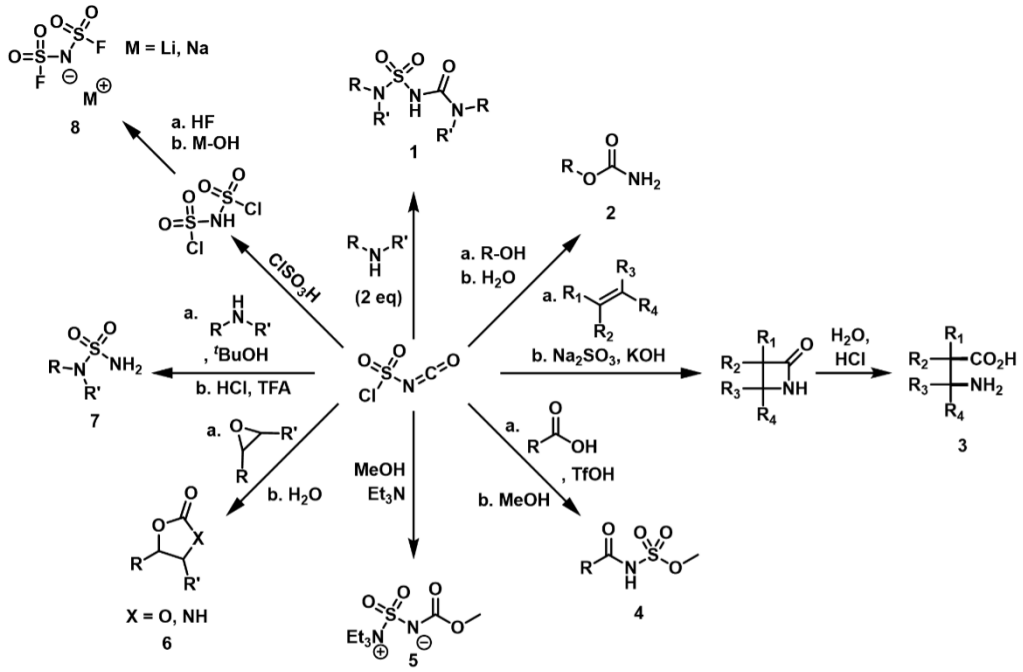
The cycloaddition of CSI to epoxides leads to five-membered cyclic oxazolidinones and carbonates (**6**).[12-13]

CSI can also react first with alcohols and subsequently with amines to generate sulfamoyl carbamates, which are eventually hydrolyzed into sulfamides (**7**). The sulfamide functional group is recently discussed as a suitable bioisosteric replacement for sulfamates, sulfonamides, ureas, carbamates and even amide functionalities. The sulfur atom presents a conformationally-rich topological arrangement of atoms when presenting itself to a protein target, and the substituents on the nitrogen atoms (up to four) offer further points of diversity.[14-15-16-17]

Another remarkable application of CSI in organic chemistry is the cycloaddition-reduction with olefins to produce ß-lactams. These compounds are attractive intermediates in the synthesis of ß-amino acids (**3**).[18-19-20]

[1] Chemam et al. Phosphorus, Sulfur Relat. Elem. 2022, 197, 8, 777-787.
[2] Graf, Chem. Ber. 1956, 89, 1071-1079.
[3] Graf, Chem. Ber. 1959, 92, 509-513.
[4] Patent publication number: CN112321462.
[5] Patent publication number: JP2004018500.
[6] Patent publication number: CN109400506.
[7] Cheraiet et al. Arch. Pharm. Chem. Life Sci. 2019, 352, 1800341.
[8] Hessainia et al. J. Heterocyclic. Chem. 2020, 57, 218-224.
[9] Atmaka et al. J. Biomol. Struct. Dyn. 2022 41, 17, 8191-820.
[10] Axthammer et al. Z. Anorg. Allg. Chem. 2016, 642, 211-218.
[11] Matoševič et al. Arh Hig Rada Toksikol. 2020, 71, 4, 285-299.
[12] Demir et al. Beilstein J. Org. Chem. 2020, 16, 1805-1819.
[13] Lorincz et al. Synth. Commun. 1986, 16, 123-130.
[14] Wang et al. J. Heterocycl. Chem. 2020, 57, 1, 151-156.
[15] Suthagar et al. Eur. J. Med. Chem. 2015, 102, 153-166.
[16] Gavernet et al. Bioorg. Med. Chem. 2007, 15, 16, 5604-5614.
[17] Ghassemi et al. Mol. Divers. 2005, 9, 4, 295-299.
[18] Atmaca et al. Arch. Pharm. Chem. Life Sci. 2019, 352, 1900200.
[19] Szakonyi et al. Amino Acid. 2011, 41, 597-608.
[20] Kardos et al. Asian J. Org. Chem. 2015, 4, 1155-1159.

Scheme 2. Selection of synthesis pathways starting from CSI towards: sulfamoylurea derivatives (1), carbamates (2), ß-amino acids (3), methyl sulfamates (4), burgess reagent (5), five-membered cyclic oxazolidinones and carbonates (6), sulfamides (7) and lithium bis(fluorosulfonyl)imide (LiFSI) (8).



A series of methyl sulfamates (**4**) was obtained in high yields under optimized conditions by reacting CSI with different commercially available aromatic and aliphatic carboxylic acids. Sulfamates play a major role in mechanistic organic chemistry, but they also have recently gained attention by pharmacologists due to their bioactive properties.[21]

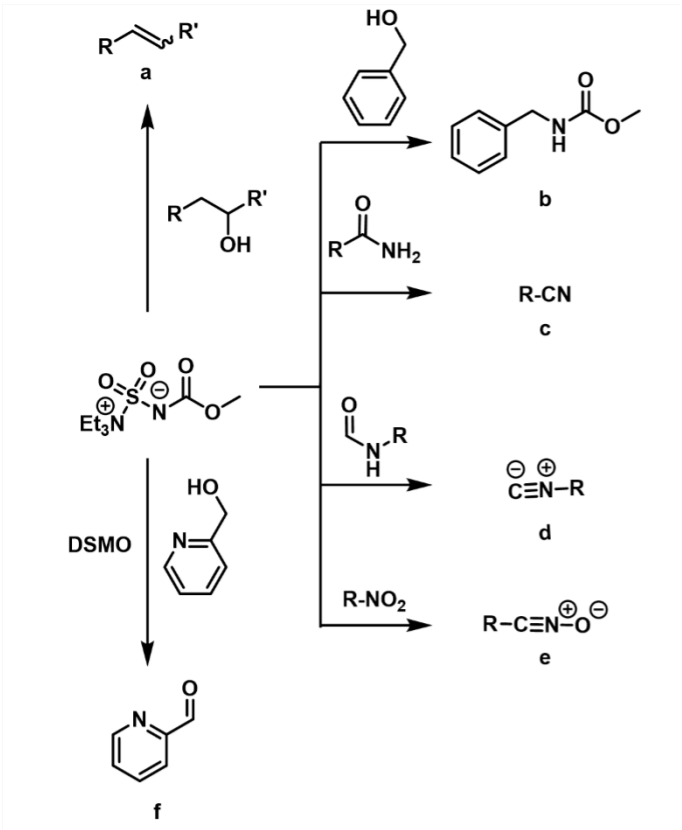
In the field of inorganic chemistry, CSI has found utility in the production of lithium bis(fluorosulfonyl)imide (LiFSI) (**8**), a promising electrolyte whose advantages, compared to other salts like $LiPF_6$, include better thermal stability, higher solubility and conductivity, lower toxicities and lower corrosion rates, better electrochemical performance, wider operating temperature, and an ability to form good solid-electrolyte interphase (SEI) layer on electrodes.[22-23-24-25-26]

Finally, CSI is the starting material in the preparation of the Burgess reagent (**5**) [methyl N-(triethylammonium)sulfonyl carbamate], which is chemically a carbamate and an inner salt. It appears as a white crystalline solid and has historically found utility (Scheme 3) as a dehydrating agent to convert secondary and tertiary alcohols with an adjacent proton into alkenes (a) (the reaction with primary alcohols generates carbamates (b)). It is also used in the dehydration of primary amides, formamides and primary nitroalkanes to generate nitriles (c), isocyanides (d), and nitrile oxides (e) respectively.[27]

[21] Atmaca et al. Tetrahedron. 2019, 75, 130467.
[22] Song et al. J. Power Sources Adv. 2022, 14, 100088.
[23] Singh et al. J. Fluor. Chem. 2019, 226, 109333.
[24] Zhong et al. J. Mater. Chem. A, 2019, 7, 24251-24261.
[25] Patent publication number: CN106044728A.
[26] Patent publication number: CN102917979B.
[27] Khapli et al. J. Indian Inst. Sci. 2001, 81, 461-476.

The Burgess reagent is soluble in common organic solvents and is prepared by addition of methanol and triethyl amine to CSI.[28] This reagent may be also used to oxidize primary and secondary alcohols to their corresponding aldehydes and ketones in DMSO (f) without the generation of toxic byproducts.[29] These oxidations were found to be rapid under mild conditions and to have excellent yields. Several reviews detailing the Burgess reagent behavior have been published, and it has found application in the total syntheses of a variety of natural compounds.[30-31]

Scheme 3. Applications of the Burgess reagent to access alkenes (a), carbamates (b), nitriles (c), isocyanates (d), nitrile oxides (e) and aldehydes (f).



In conclusion, we have presented CSI as a versatile reagent that can give rise to many organic chemistry reactions under relatively moderate conditions. CSI is commercially available at Arxada. Arxada`s CDMO team has access to the internal produced CSI and can carefully handle the reagent in further reactions. It undergoes diverse reactions, yielding valuable products such as sulfamoylurea derivatives and carbamates. CSI serves as a pivotal precursor in crafting the versatile Burgess reagent, essential in organic synthesis for processes like dehydration and oxidation. Lastly, CSI finds utility in inorganic chemistry, notably in the production of lithium-ion battery materials.

[28] Atkins et al. J. Am. Chem. Soc. 1968, 90, 17, 4744-4745.
[29] Sultane et al. J. Org. Chem. 2017, 82, 2, 1046-1052.
[30] Beemelmanns et al. Angew. Chem. Int. Ed. Engl. 2010, 49, 8021-8025.
[31] Yokoyama et al. Tetrahedron. Asymmetr. 2004, 15, 2817-2820.

Acknowledgments

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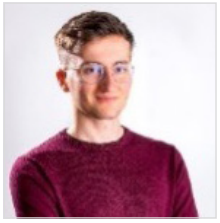

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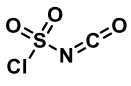
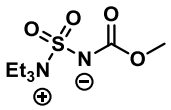
Our offer



CSI



Burgess reagent

- **One-step synthesis of CSI from kg to mt**
- **Synthesis of Burgess reagent**
- **Cyanogen chloride backward integrated**
- **Ability to derivatize on-demand**
- ***Focus on what matters to you***

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