NITRILES AS MULTIPURPOSE REAGENTS FOR THE SYNTHESIS OF SULTAMS AND SULTONS (REVIEW ARTICLE)

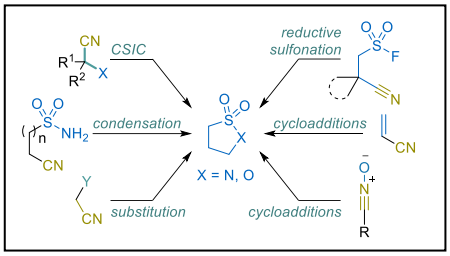
Maksym S. Kovalov[1,2], Bohdan V. Vashchenko[1,2]*

[1]*Enamine Ltd. (www.enamine.net), Chervonotkatska Street 78, Kyiv 02094, Ukraine*

[2]*Taras Shevchenko National University of Kyiv, Volodymyrska Street 60, Kyiv 01601, Ukraine*

e-mail: vashchenko@knu.ua

In this review, we discuss the use of the nitrile function in the synthesis of cyclic sulfonamides (sultams), an important class of antibiotics The cyano group is a versatile building block in sultam synthesis. It can form the sultam and sulton skeleton or activate adjacent positions. Commonly, the nitrile group undergoes the CSIC reaction, acting as an electrophilic center attacked by a carbanion, forming enamines. Nitriles also facilitate α-position substitutions through alkylation or cyclization and activate unsaturated bonds in various cycloadditions. Literature indicates the nitrile group, as a methyleneamine precursor, shows promise for sultam synthesis. This method could efficiently produce spirocyclic sultams with applications in chemistry and biology.



Keywords: sultam, nitrile, cyano group, cyclization, sulfonamides

1. RETROSPECTIVE AND PERSPECTIVES OF SULTAMS IN SYNTHETIC AND MEDICINAL CHEMISTRY

Bioisosteric replacement serves as a fundamental approach in modern synthetic and medicinal chemistry, plays a pivotal role in the design of mimetics.[1] This approach has garnered widespread recognition in the scientific community due to the extensive practical application in the development of next-generation pharmaceuticals.[2] Numerous studies show that the incorporation of bioisosteric moieties leads to enhanced selectivity, pharmacokinetic properties, as well as affinity and efficacy of drug candidates.[1,3]

The ubiquitous presence of the amide group within important natural and synthetic molecules has made it one of the most prevalent structural motifs among FDA-approved drugs.[4] This fact advocates the reasonable exploration of isosters of amides in classical and modern drug design. Among these analogs, the S(VI)-containing sulfonamide moiety emerges as the most commonly utilized isostere of the amide bond, as supported by various physicochemical parameters (Figure 1).[5]

The discovery of sulfanilamide **1** in 1908 and subsequent research on prontosil **2** in 1932, both containing the SO_2NH_2 group, marked a seminal milestone in drug development.[6] Sulfonamides have since emerged as essential compounds in the pursuit of novel therapeutics, with approximately a hundred FDA-approved drugs currently available on the pharmaceutical market (Figure 1).[6–10] The aformentioned derivatives made a class of sulfonamide antibiotics (known as "sulfa drugs"), which was then expanded by derivatives extensively used for several decades, e.g. sulfamethoxazole **3**, acetazolamide **4**, and celecoxib **5**.

Cyclic sulfonamides, also known as sultams, represent a promising class of organic compounds garnering significant attention across scientific and industrial scientific domains due to their remarkable biological activities.[6–10] Sultams itself find utility as valuable reagents[11–13] and catalysts for asymmetric transformations with a prominent example of camphorsultam **6**[14,15].

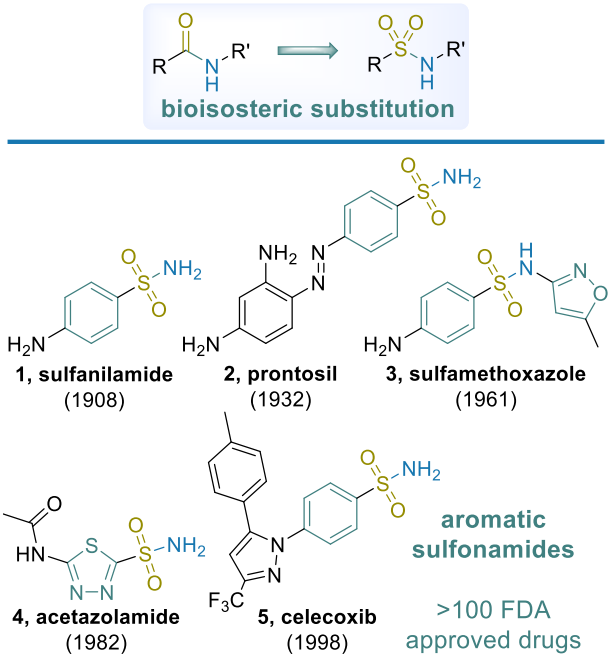


Figure 1. Bioisosteric replacement of amides with sulfonamides, and prominent examples of sulfa drugs

Among the most renowned cyclic sulfonamides is saccharin **7**, a pioneering artificial sweetener widely utilized throughout the 20th century (Figure 2).

Sultams display a diverse range of biological activities, including antibacterial, antibiotic, anticancer, antifungal, antipsychotic, antiviral, biostimulating, cardioprotective, cytotoxic, fungicidal, and mucotoxic activities.[6–10,16] Notably, sultam inhibitors targeting the interaction between integrins and endothelial immunoglobulins have therapeutic potential for inflammation and autoimmune diseases,[17,18] while β-secretase inhibitors show promise in the treatment and prevention of Alzheimer's disease.[19] Moreover, sultam derivatives have demonstrated efficiency in the treatment of lipidemias, associated with abnormal levels and metabolism of lipoproteins in the bloodstream.[20] Other notable examples include the cyclooxygenase-2 inhibitor ampiroxicam **8** (COX-2)[21], the glaucoma treatment drug brinzolamide **9**[22], and benzodithiazine dioxide **10** exhibiting antiviral and anticancer activities.[23]

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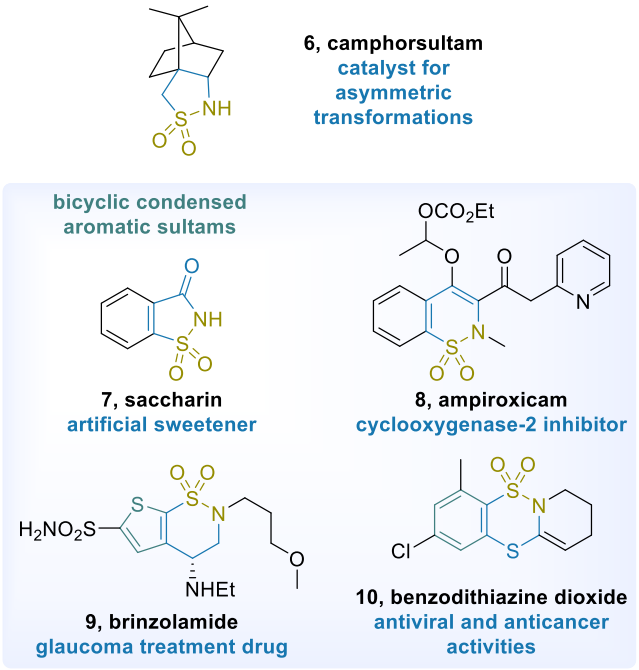

Figure 2. Prominent sultam representatives: synthetically valuable camphorsultam (**6**), saccharin (**7**), and representative drugs with the sultam moiety **8–10**

At present, the development of medicinal relevant products relies on well-defined criteria and requirements to optimize physicochemical characteristics of drug candidates. Novel approaches in organic synthesis heavily rely on the lead-oriented synthesis concept introduced in 2012,[24] which outlines stringent criteria for favorable physicochemical and structural characteristics that facilitate the direct use of compounds in the initial stages of the drug development. Churcher and co-workers proposed criteria for the lead compounds encompassing molecular weight (MW = 200…350), lipophilicity (Log*P* = –1…3), etc.

An additional criterion pertains to three-dimensionality and conformational restriction, commonly known as "escape from flatland".[25] This principle advocates the transition from planar aromatic structures to sp^3-enriched three-dimensional analogs, thereby improving the pharmacokinetic characteristics of potential drugs.[26]

After the introduction of the concept of lead-oriented synthesis and the shift from planar aromatic fragments to the saturated counterparts, the scientific community's focus turned towards small saturated molecules. These derivatives increasingly utilized as fragments, building blocks, or scaffolds in the design of biologically active compounds. This paradigm extended to the chemical space of sulfonamides, which were predominantly aromatic derivatives (including compounds **1**–**5**), and sultams, primarily represented by derivatives of saccharin **7** and related aromatic systems **8**–**10**.[27–29] Consequently, sp^3-enriched saturated and partially unsaturated scaffolds have emerged as promising examples accompanying the current tendencies in drug design.[30] Notably, the list of saturated sultams includes the anticonvulsant drug sulthiame **11**,[31] a combination of acyclic and cyclic sulfonamides, specifically 1,2-thiazinan-1,1-dioxide (Figure 2). Some articles have explored distinct categories of other sultams,[32] e.g. chiral auxiliary sultams with scaffolds other than camphor,[33] benzothiazines,[34] or bridging sultams featuring a nitrogen atom in the bridgehead position.[35] Additionally, *N*-substituted isothiazolidine-1,1-dioxide (γ-sultam) is exemplified by the antidiabetic agent **12** (Figure 3).

Meanwhile, numerous examples of low-molecular-weight compounds employed as active drugs possess a rigid, conformationally restricted structure.[26,36] Conformationally rigid systems, e.g. fused, bridged, and spirocyclic fragments containing small and/or medium cycles, are highlighted for their unique attributes,[37–41] including bioresistance, metabolic resistance at physiological pH values, etc.

Over the past 20 years, leading pharmaceutical companies (BMS, Takeda, Merck & Dohme, etc) have shown increasing interest in saturated conformationally rigid bicyclic fused sultams, which exhibit remarkable anticancer activity and have been studied as potential antischizophrenic and antithrombotic agents (Figure 3). The vast majority of synthesized and patented sultams are decorated with a fused saturated sulfonamide fragment. Notable examples of of [m.n.0]sultams include an antischizophrenic agent **13**, an antithrombotic agent **14**, an anticancer agent **15**, a protease-activated receptor 1 (PAR-1[42]) antagonist **16**, a γ-secretase inhibitor **17**,[43] and a casein kinase II inhibitor **18**.[44] Conversely, bicyclic bridged and spirocyclic sultams are less studied, likely due to the limited number of synthesized representatives to date, and the scarcity of described preparation methods compared to their fused counterparts. This chemotype is represented by a human immunodeficiency virus protease inhibitor **19**[45] and a related orphan retinoic acid receptor-related orphan receptor γ[46] (RORγ) inhibitor **20**.

Additional interest in saturated sultams has rised from their advantageous physicochemical properties. Unlike azetidines, pyrrolidines, piperidines, etc., sultams demonstrate lower basicity, increased aqueous solubility, easy modification via *N*-alkylation, non-planar three-dimensional structure, as well as resistance to protease-catalyzed cleavage. Notably, γ-sultams closely resemble pyrrolidines in conformation, rather than their direct isosteric analogs - γ-lactams (pyrrolidones) with a flat amide moiety, therefore providing higher three-dimensionality. Theoretical studies[47–50] and experimental data[51–55] have demonstrated distinct conformational properties between amide and sulfonamide groups. Amide fragments typically adopt a planar configuration (torsion angle of the amide bond at 0° or 180°), while sulfonamides mainly exist in synclinal or anticlinal conformations (with corresponding torsion angles of ±60° and ±100°). Furthermore, the sulfonamide nitrogen atom exhibits non-planarity, characterized by significant pyramidization.

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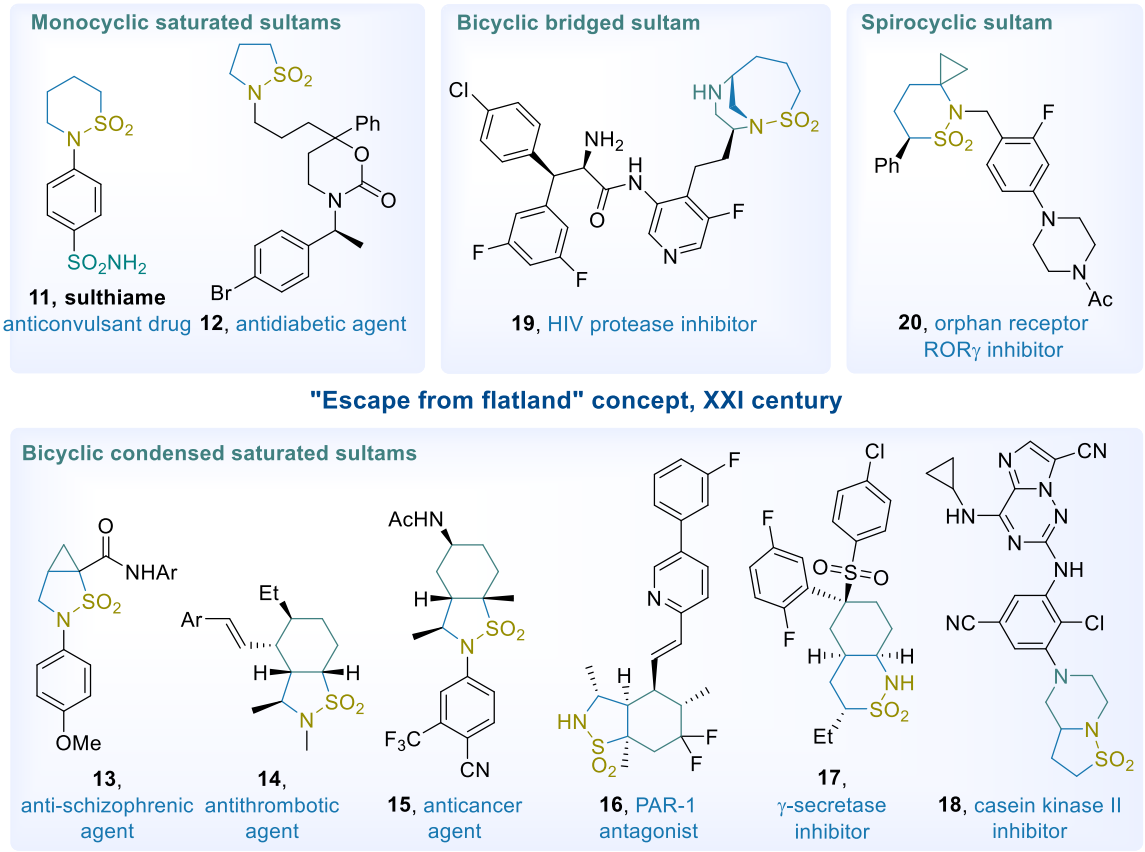

Figure 3. Saturated with mono- and bicyclic salums **11–20**

Therefore, sultams can be considered bioisosteres of lactams, accounting for a certain degree of conformational divergence (Figure 4). For instance, β-keto-γ-sultams are widely regarded as bioisosteres of tetramic acid **21**.[56] The corresponding ketosultam derivatives demonstrate efficacy in treating inflammation and autoimmune diseases due to their potent inhibitory effect on the adhesion of immunoglobulin LFA-1 (integrin $\alpha_L\beta_2$) to its ligand ICAM-1 (molecule of intercellular adhesion 1, also known as CD54).[57] Other functionalyzed derivatives with amino- and alkoxy carbonyl groups attached to the sultam skeleton has also been enlightened (**Figure 5**). Notably, compound **22**, bearing an ester residue at the C-3 position exhibits notable antimycobacterial activity, particularly against *Mycobacterium tuberculosis* and *M. kansasii*.

In turn, compounds **23** and **24** (ATSAO-T) were studied as reverse transcriptase inhibitors against human immunodeficiency viruses (HIV-1, III_B and HIV-2, ROD) in human T-lymphocytes (MT-4). Notably, the oxygen-containing analogs of sultams, e.g. cyclic sulfonates (sultones), exhibited superior efficacy against DNA viruses or retroviruses under specific conditions. Among the tested compounds, sultone **25a** (TSAO-T) and its *N*-methyl-substituted derivative **25b** (TSAO-m3) demonstrated significant activity, surpassing aza-analogs **24** with an EC_{50} 0.057 μM against HIV-1 (HIV-1, III B) and HIV-2 (HIV-2, ROD) in human T-lymphocytes (MT-4, T-cells).[58] Additionally, certain 3,3,6-trisubstituted pyridosultones **26** emerged as potent inhibitors of HIV-1 (HIV-1, III B) with EC_{50} 17–22 μM.[59] However, their anti-HIV-1 activity was up to three orders lower than that of TSAO-m3 and TSAO-T. These pyridosultones **26**, however, exhibited considerable activity against vesicular stomatitis virus and respiratory syncytial virus. In turn, the related monocyclic sultone **27** demonstrated significant activity against human cytomegalovirus and varicella virus.

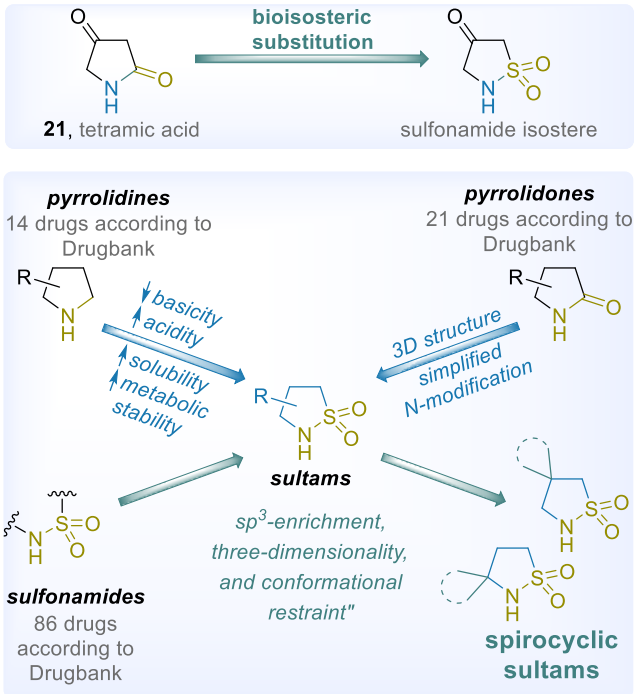

Figure 4. Sultams as bioisosteric analogs of saturated azaheterocycles and lactams

Among specific physicochemical features of sultons, the use of saturated γ-sultone **28** and its homologs as alkylating agent is widely reported, while this property is not characteristic for its aza-analogs (Figure 6).[60]

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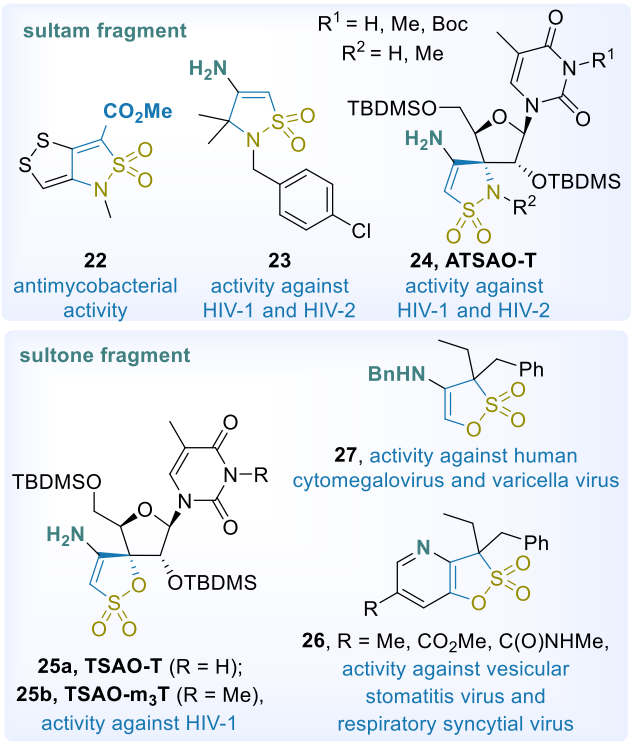


Figure 5. Antibacterial and antiviral γ-sultams **22**–**24** and γ-sultones **25**–**27**

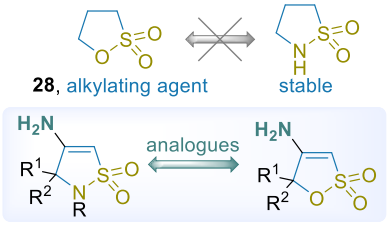


Figure 6. Sultons as analogs of sultams

At the same time, partially unsaturated sultones lack the alkylating ability due to the presence of a conjugated fragment.[61] As a result, partially unsaturated conjugated sultones could be considered as analogs of partially unsaturated sultams by their chemical behavior.

Given the significance of sultams and sultones in modern synthetic and medicinal chemistry, numerous methods have been developed for their synthesis. These methods predominantly involve the formation of S–N bonds through intramolecular sulfonylation or the formation of other bonds within the sultam fragment (N–C, S–C, and C–C) primarily through alkylation reactions. In most cases, the synthesis requires the use of bi- and polyfunctionalized compounds with reactive groups suitable for cyclization. The other option relied on the presence of the activating groups.

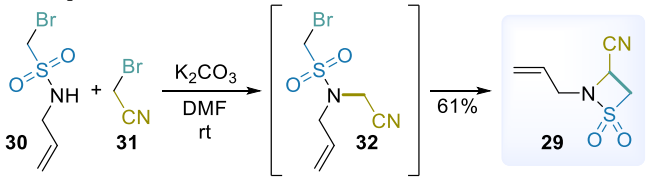
According to the literature data, among all electron-withdrawing groups, nitrile fragment is of particular interest in the synthesis of sultams, since it undergoes a wide range of chemical transformations at both carbon and nitrogen atoms. Additionally, the nitrile group activates neighboring positions with the most prominent examples of compound with activated methylene unit for classical alkylation and condensation reactions.

Therefore, this review focuses on methods for the synthesis of sultams and sultones that involve transformations of nitriles, wherein the cyano group could either directly react in the formation of a cyclic sulfonamide or act as an activating group. Most chemical transformations of nitriles in the synthesis of sultams and sultones rely on inter- and intramolecular reactions of sulfonamides with an additional electrophilic center, i.e. carbonyl (aldehydes, ketones, esters), halide, sulfonate groups, oxirane, or other nitrile fragment. A well-studied transformation in this context is the CSIC reaction (Carbanion-mediated Sulfonate (Sulfonamide) Intramolecular Cyclization), when the nitrile carbon atom becomes a part of the heterocyclic skeleton via the intramolecular Thorpe condensation.[62–64] Various examples also involve cyclization via Michael addition, as well as cycloaddition reactions, that are widely utilized for constructing fused sultams.

2. THE NITRILE GROUP AS AN ACTIVATOR IN THE CONSTRUCTION OF HETEROCYCLE

2.1 Cyclization via intramolecular nucleophilic substitution

An illustrative example of the activation of adjacent positions in the carbon chain by an electron-accepting nitrile group is observed in the synthesis of β-sultam **29**. This process involves the reaction of sulfonamide **30** with bromoacetonitrile **31** (Scheme 1).[65] Initially, the *N*-alkylation of the sulfonamide takes place in the presence of K_2CO_3 in DMF, resulting in the formation of intermediate compound **32**, which can be isolated from the reaction mixture. Subsequently, deprotonation of the α-methylene unit in **32** occurs, and the resulting carbanion acts as a nucleophile, leading to the replacement of bromine and the subsequent formation of **29**.



Scheme 1. Alkylation of allyl sulfonamide with bromoacetonitrile **31** followed by intramolecular nucleophilic substitution for the synthesis of β-sultam **29**

2.2 Synthesis of fused sultams via 1,3-dipolar [3+2] cycloaddition reaction.

One of the prominent strategies for constructing fused sultams, particularly five-membered derivatives, involves the 1,3-dipolar [3+2] cycloaddition reactions. This transformation relies on the use of partially unsaturated sultams featuring an imine bond C=N, which acts as a 2π-electron component (Scheme 2).[66] For instance, the imine derivative of saccharin **33** undergoes a palladium-catalyzed enantioselective annulation reaction with nitrile-substituted allylsilane **34**, serving as a precursor of trimethylene methane (2π-electron component). This results in the formation of a pyrrolidine ring **35**. Compound **34** contains trimethylsilyl (TMS) and acetate (OAc) groups, which undergo cleavage upon the action of a palladium catalyst in the presence of ligand **36**. Consequently, a three-center two-electron bond forms with palladium, along with a carbanion stabilized by a nitrile group, which then nucleophilically attacks the imine carbon atom, leading to further cyclization into a tricyclic sultam with high enantio- and diastereoselectivity (85% yield).

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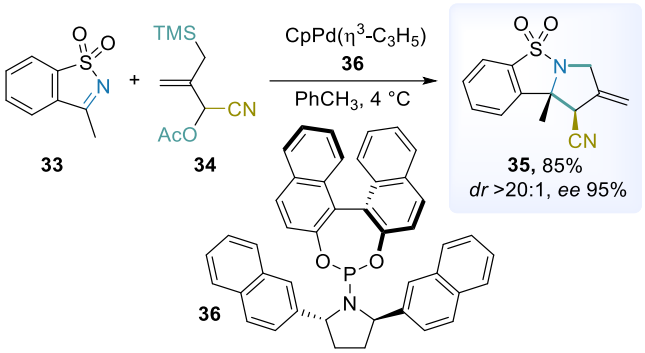
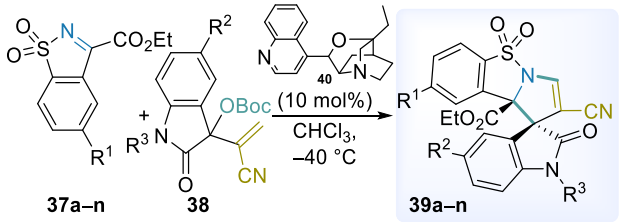


Scheme 2. 1,3-Dipolar cycloaddition with trimethylenemethane precursor **34** for the synthesis of tricyclic sultam **35**

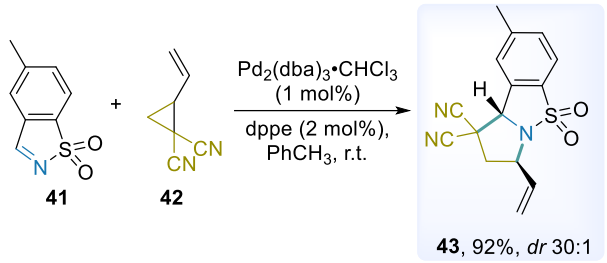
Another notable application of benzoisothiazole derivatives **37a–n** involves enantioselective organocatalytic cycloaddition reactions with derivatives **38** to give azaspirooxyindole derivatives **39a–n**, featuring a fused sultam fragment. The alkaloid organocatalyst **40**, containing a tertiary amine moiety as the main functional group, interacts with substituted acrylates **38**. Subsequent transformations involve the removal of *O*-Boc group and the formation of anions, which then attach to the imine carbon of sultams **37**. The final step entails the replacement of the alkaloid moiety with the sulfonamide nitrogen atom, leading to cyclization and the formation of spirocyclic derivatives **39** (Table 1).[67]

Table 1. Synthesis of azaspirooxyindole derivatives **40a–n**



Product	R^1	R^2	R^3	Yield 39, %	*dr*	*ee*, %
39a	H	H	Bn	95	>20:1	98%
39b	Me	H	Bn	98	>20:1	95
39c	OMe	H	Bn	98	>20:1	97
39d	Cl	H	Bn	86	>20:1	97
39e	F	H	Bn	88	>20:1	97
39f	H	Br	Bn	92	9:1	97
39g	H	OMe	Bn	93	>20:1	98
39h	H	F	Bn	91	>20:1	97
39i	H	OCF_3	Bn	94	>20:1	97
39j	H	Cl	Bn	95	>20:1	98
39k	H	NO_2	Bn	95	>20:1	98
39l	H	I	Bn	97	>20:1	96
39m	H	H	Me	92	>20:1	96
39n	H	H	Allyl	95	>20:1	98

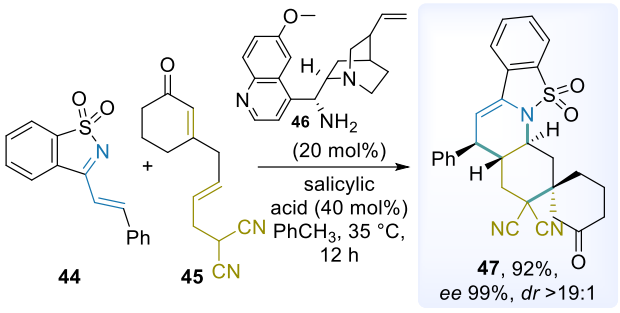
Furthermore, another annulation reaction utilizes sulfoimine **41** and involves the use of vinylcyclopropane **42**, wherein the strained cycle undergoes opening under the action of a palladium catalyst. Consequently, a carbanion stabilized by two nitrile groups is formed, which subsequently attaches to the imine, leading to cyclization and the formation of tricyclic sultam **43** (Scheme 3).[68]



Scheme 3. Palladium-catalyzed 1,3-dipolar cycloaddition-annealation of vinylcyclopropane **42** and unsaturated sultam **41** for the synthesis of **43**

2.3 Synthesis of fused sultams via cascade transformations with the key [4+2] cycloaddition

The [4+2] Diels-Alder cycloaddition reaction represents a widely used method in both classical and modern organic chemistry for constructing cyclic systems. An intriguing approach includes the use of azadienes for the aza-Diels-Alder reaction as a key step of the transformation.[69] For instance, β-styrylsaccharin **44** is involved in a cascade asymmetric organocatalytic reaction with 2,5-dienone **45**, featuring a reactive malononitrile fragment. Using of salicylic acid in toluene and quinine derivative **46** as a catalyst, the corresponding polycyclic product **47** could be obtained in enantiomerically and diastereomerically pure form (Scheme 4).[70]



Scheme 4. Cascade reaction of aza-Diels-Alder with the formation of sultam **47**

2.4 Cyclization of 2-chloro-3-phenylpropanenitriles into 3,4-dihydro-2*H*-benzo[*e*][1,2]thiazine-1,1-dioxides

The sulfonamide nitrogen atom is typically considered a relatively weak nucleophile. Nevertheless, in certain scenarios its nucleophilicity can be enhanced towards commonly encountered reactive electrophiles, i.e. as carbonyl derivatives, nitriles, halides, etc., and could be used for the intramolecular transformations leading to sultams. The representative reaction sequence relied on the use of sulfonyl chloride **48**,m in turn synthesized from the α-chloronitrile **49** via a chlorosulfonylation reaction, accompanied by simultaneous hydrolysis of the nitrile to the amide. Upon treatment with an amine, the sulfonamide formed undergoes cyclization, resulting in the formation of sultam **50**. Subsequent transformations include the alkaline hydrolysis of amide **50** to the corresponding carboxylic acid **51** (Table 2).[71]

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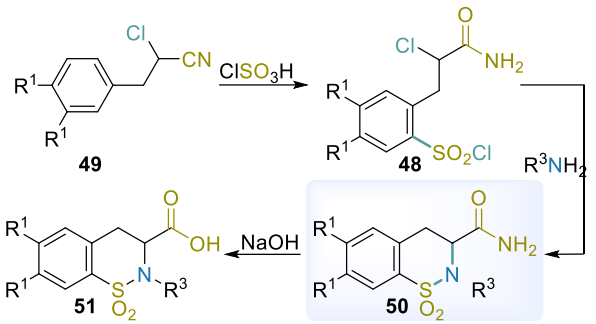
Table 2. Synthesis 3,4-dihydro-2*H*-benzo[*e*][1,2]thiazine-1,1-dioxides **50** and **51**



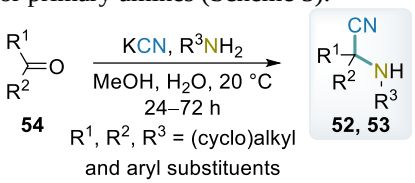
N	R^1	R^2	R^3	Yield 48, %	Yield 50, %	Yield 51, %
1	OMe	OMe	H	41	37	84
2	OMe	OMe	Me	41	59	96
3	OCH_2CH_2O		H	51	44	91
4	OCH_2CH_2O		Me	51	88	92
5	Cl	H	Me		49	86[A]
6	Cl	Cl	Me	89	36	100[B]

[A] hydrolysis was carried out under acidic conditions using H_2SO_4 instead of alkali; [B] hydrolysis was carried out under acidic conditions using HCl instead of alkali

3. CYCLIZATIONS BY THE ELECTROPHILIC CARBON ATOM OF THE NITRILE GROUP

3.1 CSIC reaction as the common method for obtaining sultams from aminonitriles

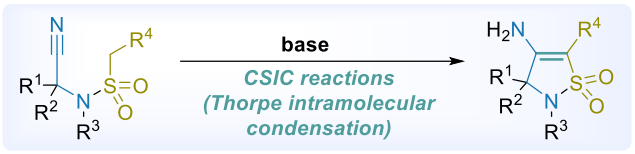
Typical starting materials utilized for the synthesis of functionalized γ-sultams[61] are aminonitriles **52** (alicyclic derivatives) and **53** (cyclic compunds), readily available products of the Strecker reaction of **54** with cyanides and ammonia or primary amines (Scheme 5).



Scheme 5. The Strecker reaction for the synthesis of aminonitriles **52** and **53** as precursors of CSIC reaction

The synthesis of sultams, particularly bicyclic ones,[72] via the CSIC reaction has gained widespread use, especially over the last 10 years.[63,72–75] The utilization of *N*-sulfonylated α-aminonitriles was first explored by Marco-Contelles and co-workers,[61,74] and the term "CSIC reaction" was introduced to the literature in 2003, although similar reactions were published three decades earlier, including the condensation of sultams with nitriles to give enamines.[76] This transformation proceeds analogously to intramolecular nucleophilic addition to enolates and aldol condensation of alkanesulfonates (sulfonamides) with the formation of sultones (sultams).[63,77–79] The reaction is facilitated by the high α-*CH*-acidity of the methylene unit near the sulfonamide group, and in the absence of more mobile sulfonamide *NH* protons, which could be deprotonated first.

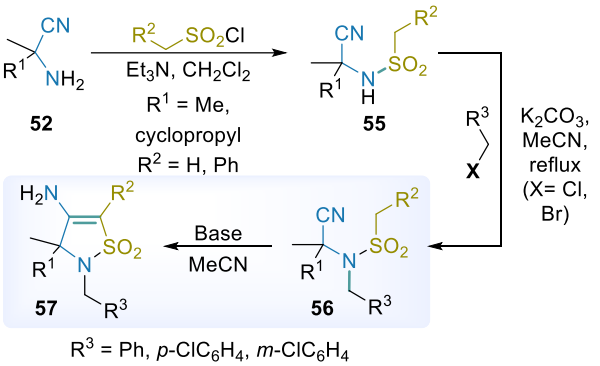
The widespread application of CSIC approach is facilitated by the availability of reagents and the ease of obtaining them from commercially available compounds, e.g. amino and hydroxy acids,[63] corresponding nitriles,[63,80,81] etc.[82–84] Thus, CSIC reaction has become the primary method for obtaining 4-amino-2,3-dihydroisothiazole-1,1-dioxides (enaminosultams) from cyanosulfonamides (Scheme 6). As it was mentioned above, these compounds have a great potential for biological activity, making them intriguing candidates for drug development.[85]



Scheme 6. CSIC reactions (intramolecular Thorpe condensation) for the synthesis of enaminosultams

The sulfonylation reaction of aminonitriles **52** is carried out by the action of sulfonyl chlorides in the presence of an organic or inorganic base for deprotonation (Table 3). For example, the common method described by Marco-Contelles and co-workers[61,74,86,87] involves the sulfonylation of aminonitriles **52** with mesyl chloride (MsCl) or benzylsulfonyl chloride ($BnSO_2Cl$) in the presence of triethylamine (Et_3N) as a base in dichloromethane (CH_2Cl_2).

Table 3. Synthesis of β-enaminosultams **57**



N	Base	R^1	R^2	R^3	Yield 57, %
1	NaH	Me	H	Ph	65
2		Me	H	*p*-ClC_6H_4	43
3		Me	H	*m*-ClC_6H_4	43
4		cyclopropyl	H	Ph	91
5	DBU	Me	Ph	Ph	75
6		Me	Ph	*m*-ClC_6H_4	47

For the further construction of the γ-sultam system, cyano sulfonamides **55** were subjected to *N*-alkylation using BnBr or isomeric chlorobenzyl derivatives (*p*- or *m*-$ClC_6H_4CH_2Cl$) in the presence of K_2CO_3. This process led to the formation of tertiary cyano sulfonamides **56**,[74] which are then involved in the carbanyonic cyclization to give 4-amino-2,3-dihydroisothiazol-1,1-diones **57** in the presence of 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU),[74] NaH or Cs_2CO_3.[74,86] The literature sources highlighted that attempts to synthesize β-enaminosaltums **57** with an unsubstituted nitrogen atom in the 1-position of the heterocyclic fragment from secondary sulfonamides **56** were unsuccessful due to the presence of an acidic *NH* proton of the secondary sulfonamide group.[74,86]

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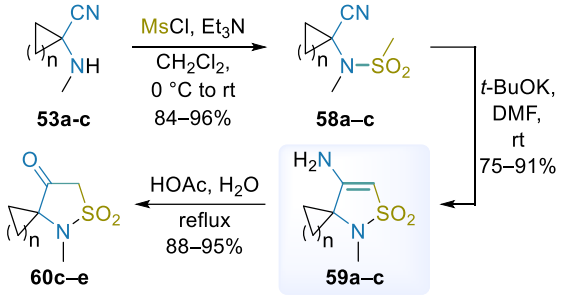
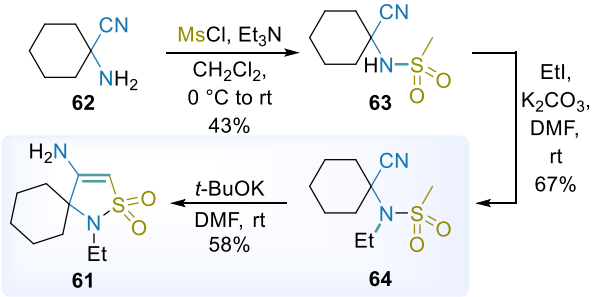
Mesylation of cyclic aminonitriles **53a–c** led to the formation of sulfonamides **58a–c**, which were subjected to carbanion cyclization for the synthesis of spirocyclic β-enamino-γ-sultams **59a–c** using *t*-BuOK as a base in DMF (Table 4).[87] Notably, β-enamino-γ-saltams **59a–c** could be readily transformed into the corresponding β-keto-γ-saltams **60a–c** in up to 95% yield.[87]

Table 4. Synthesis of β-enamino-γ-sultams **59a–c** and β-keto-γ-sultams **60c–f**



N	n	Compound	Yield 58, %	Yield 59, %	Yield 60, %
1	3	**a**	65	78	88
2	4	**b**	82	84	95
3	5	**c**	20	56	92

Moreover, this approach allows for the introduction of other alkyl groups near the sultam nitrogen atom. For instance, *N*-ethyl-substituted spirocyclic sultam **61** was synthesized from 1-aminocyclohexanecarbonitrile **62** via sulfonylation (43% yield). Sulfonamide **63** thus obtained was subjected to alkylation with ethyl iodide to give sulfonamide **64**. This compound serves as a precursor for cyclization to the corresponding sultam **61** upon the action of *t*-BuOK in DMF (Scheme 7).[88]

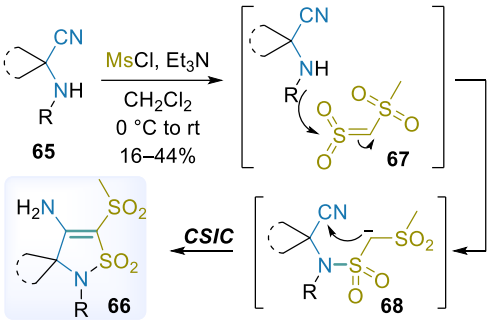


Scheme 7. Synthesis of 4-amino-1-ethyl-2-thia-1-azaspiro-[4.5]dec-3-ene-2,2-dioxide **61**

The synthetic sequence involving mesylation and carbanionic cyclization is particularly interesting for sterically hindered α-aminonitriles. Steric factor was achieved by incorporating an additional methyl group into the carbocyclic substituent or by attaching ethyl or isopropyl group to the nitrogen atom of aminonitrile. Mesylation of α-(*N*-ethylamino)- and α-(*N*-propylamino)-α,α-disubstituted aminonitriles **65a–c**, as well as their isomeric α-*N*-methyl-substituted derivatives with an additional methyl substituent in all positions of cyclopentane and cyclohexane cores of **65d–i**, resulted in the formation of alternative products of the CSIC reaction, namely β-amino-α-mesyl-γ-sultams **66a–i** in 16–44% yield (Table 5).[88]

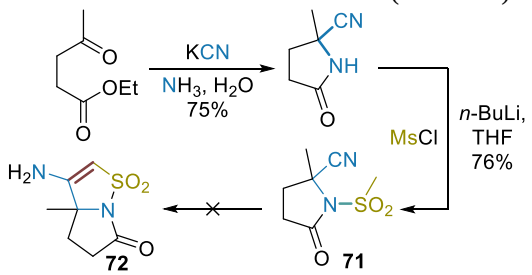
The proposed mechanism for the formation of β-amino-α-mesyl-γ-sultams **66** from sterically hindered aminonitriles **65** involves the base-catalyzed initial dimerization of mesyl chloride, leading to the formation of reactive mesylsulfene **67**. The subsequent Michael addition of aminonitriles **65** to mesylsulfene **67** proceeds through the formation of (methylsulfonyl)methanesulfonamides **68**, which are then transformed into C-mesylene amino sultams **66** via the common CSIC reaction.

Table 5. Synthesis of α-*C*-mesylated β-enamino-γ-sultams **66a–i**



N	Cyclic substituent	R	Yield of α-mesyl-γ-sultam 66, %	
1	$(CH_2)_4$	Et	**66a**	38
2		*n*-Pr	**66b**	42
3	$(CH_2)_5$	Et	**66c**	41
4		*n*-Pr	**66d**	44
5		Me	**66e**	17
6		Me	**66f**	22
7		Me	**66g**	23
8		Me	**66h**	19
9		Me	**66i**	16

Notably, the presence of conformationally rigid fragments inroduce a notable limitation to the scope of CSIC reaction. For example, cyanobutyrolactam **69**, obtained via the Strecker tandem reaction from ethyl 4-oxopentanoate **70** via the subsequent lactamization by the introduced amino group, can be easily mesylated in 76% yield. However, attempts to perform the carbanion cyclization of cyanopyrrolidinone sulfonamide **71** into **72** were unsuccessful (Scheme 8).[61]



Scheme 8. Attempted synthesis of bicyclic derivative **72**

Furthermore, the use γ-ketoester **73** in the Strecker reaction for the preparation of fused cyanobutyrolactam **74**, followed by its mesylation was successful to obtain

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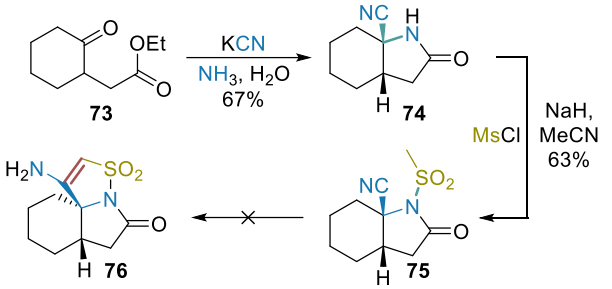
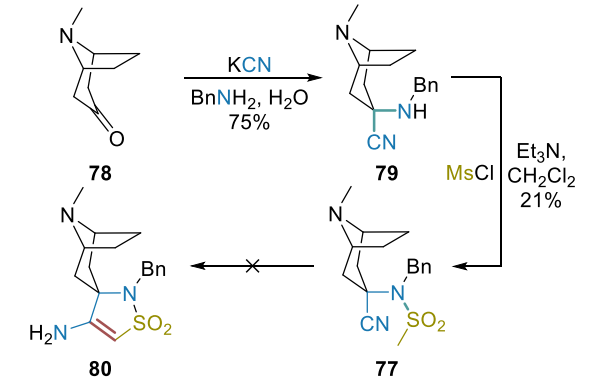
intermediate **75** (Scheme 9). However, CSIC reaction was not fruitful for **75** to form product **76** by using NaH in MeCN or DBU in MeCN at rt.[61]

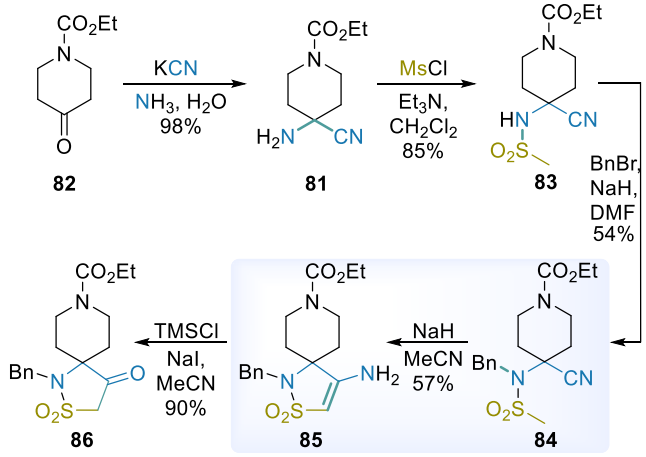


Scheme 9. Attempted synthesis of tricyclic fused sultam **76**

Another limitation involves the presence of bulky bridging fragments. For example, the CSIC cyclization of the sterically hindered *N*-mesylated aminonitrile **77** (obtained from tropinone **78** via aminonitrile **79**) in attempts to synthesize spirosultam **80** also proved unsuccessful (Scheme 10).[61] In contrast, the less rigid aminonitrile **81** (counterpart to tropinone **79** derived from piperidin-4-one **82**, lacks an ethylene bridge), readily undergoes sulfonylation and subsequent cyclization.[61]



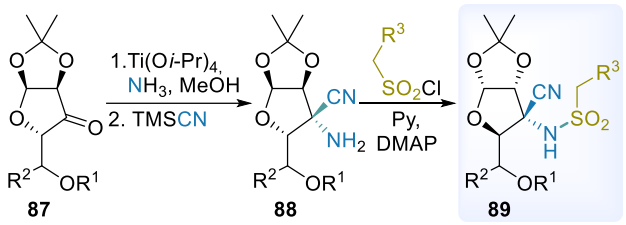
Scheme 10. Attempted synthesis of tricyclic spirocyclic sultam **80**



Scheme 11. Synthesis of spirocyclic derivatives **85** and **86**

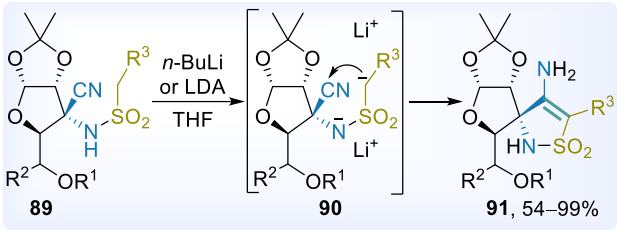
The subsequent stages involved the alkylation of sulfonamide **83** with BnBr in DMF in the presence of NaH to synthesize derivative **84**, which then underwent a CSIC reaction using NaH in MeCN at rt to form enaminosultam **85** (Scheme 11).[61] Furthermore, the synthesis of β-keto-γ-sultam **86** was demonstrated through the TMSCl-mediated transformation of enamine **85**.

Table 6. Synthesis of sulfonamides **89** from pentofurano-3-ulose **87**



N	R^1	R^2	Yield of aminonitrile **88**, %	R^3	Yield of sulfamide **89**, %
1	$C(CH_3)_2OCH_2$		80	H	80
2	Tr	H	98	H	92
3				Ph	93
4	Bn	H	70	H	98
5				Ph	98
6	Bz	H	82	H	95
7				Me	98
8				Ph	97

Table 7. CSIC reaction for the synthesis of sultam **91** via the formation of diainone **90**



$R^1 + R^2 = C(CH_3)_2OCH_2$
R^1 = Tr, R^2 = H

R^1 = Bn, R^2 = H
R^1 = Bz, R^2 = H
R^3 = H, Ph

N	R^1	R^2	R^3	Yield 91, %
1	Tr	H	H	98
2	Bn	H	H	99
3	Bz	H	H	54
4	$C(CH_3)_2OCH_2$		H	60
5	Tr	H	Ph	76
6	Bn	H	Ph	73
7	$C(CH_3)_2OCH_2$		Ph	80

Protected pentofurano-3-ulose derivatives **87** underwent conversion to aminonitriles **88** using NH_3–MeOH and $Ti(OiPr)_4$ as Lewis acid, followed by treatment with TMSCN to introduce a nitrile group (Table 6). Subsequent sulfonylation of aminonitriles **88** with mesyl chloride, ethyl or benzylsulfonyl chlorides in the presence of pyridine and DMAP proved to be an effective method for the synthesis of cyanoalkylsulfonamides **89** in high yields (80–98%). Notably, unlike intramolecular attacks of the nitrile group by carbanions of methylene-active *N*, *N*-disubstituted sulfonamides, the CSIC condensation of *N*-monosubstituted cyanosulfonamides **89** is possible under the action of a threefold excess of *n*-BuLi or lithium diisopropylamide (LDA) in THF, following *N*- and *C*-deprotonation reactions. Excess of bases are necessary in this step due to the presence of the acidic *NH* proton of the secondary sulfonamide fragment **89** and the formation of the *N*-lithium salt **90**, which could be then proceed to *C*-deprotonation. The subsequent cyclization of the formed dianions **90** serves as a successful

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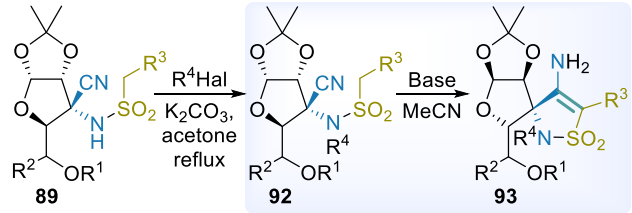
approach for the synthesis of 4-aminosultams **91** in 60–98% yield (**Table 7**). As it was previously mentioned, these 4-aminosultams, i.e. ATCAO-T and related compounds, serve as important precursors for the synthesis of various pharmaceutical agents.[58,62–64,85,89]

Alkylation reactions of cyanosulfonamides **89** are feasible, specifically with methyl iodide, benzyl bromide, or allyl bromide, by reflux in acetone in the presence of K_2CO_3 to give sulfonamides **92** in 25–80% yield (Table 8). The subsequent cyclization of the *N*-substituted sulfonamides **92** into the corresponding *N*-substituted sultams **1.63** could be achieved using either Cs_2CO_3 or NaH in MeCN to give products in 25–96%. It was observed that in the case of using Cs_2CO_3, the yields are higher (up to 90%), compared to NaH (35–61% yield). To achieve a complete conversion of **92** into the cyclic derivatives **93**, the reaction time needs to be extended to 48 h.[62,85,89] The use of Cs_2CO_3 resulted in improved yields, and this method has been extended to a larger number of products (25–96% yield).

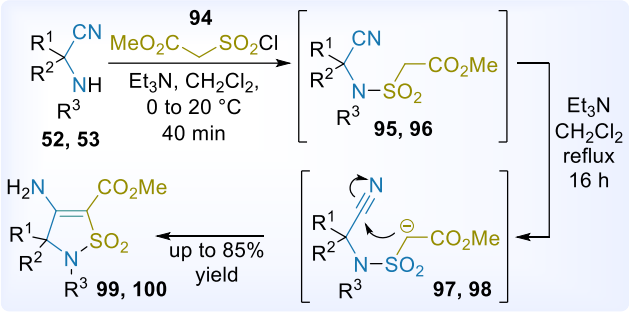
Table 8 . Synthesis of *N*-substituted sultams **93**



N	R^1	R^2	R^3	R^4	Yield 92, %	Base	Yield 93, %
1	$C(CH_3)_2OCH_2$		H	Me	95	Cs_2CO_3	40
2			H	allyl	76		66
3			H	Bn	78		96
4			Ph	Bn	16		79
5	Tr	H	H	Me	98	NaH	61
6						Cs_2CO_3	90
7			H	allyl	56		95
8			H	Bn	66		46
9			Ph	allyl	47		89
10			Ph	Bn	42		46
11	Bn	H	H	Me	96	NaH	35
						Cs_2CO_3	33
12	Bz	H	H	Me	98		25

A novel method for the sulfonylation of aminonitriles **52** and **53** using methyl-2-(chlorosulfonyl)acetate **94** has been developed under standard conditions. The process involves the use of a threefold excess of Et_3N in CH_2Cl_2 at 0 °C to rt and further reflux (Scheme 12).

At the first step, acyclic cyanosulfonamides **95** or their monocyclic derivatives **96** are formed without separation from the reaction mixture. These intermediates then rapidly undergo the subsequent CSIC process, wherein Et_3N catalyzes the formation of carbanions **97** or **98**, leading to cyclization and the formation of 5,5-dialkyl- or 5,5-methylphenyl-substituted **99** and spirocyclic **100** γ-sultamcarboxylates. The complete conversion of sulfonamides **95** and **96** into CSIC reaction products is achieved by refluxing the reaction mixture for 4 h. This results in the synthesis of enaminosultam carboxylates **99** and **100** in 8–85% yield.[90]



R^1 = Me, Et, Ph; R^2 = Me, Et, Ph; $R^1 + R^2 = (CH_2)_n$, n = 4–6; R^3 = Me, Bn, Ph

Scheme 12. One-pot synthesis of β-enamino-γ-sultam-α-carboxylates **99** and **100**

The experimental results confirmed that intermediates **95** and **96** are highly reactive. When the reaction time is over 40 minutes or the temperature is raised above 0 °C, a rapid CSIC reaction takes place, leading to the formation of sultamcarboxylates.

The influence of steric factors on the formation of **99** and **100** was studied by changing the size of the substituents present in the starting aminonitriles **52** and **53** near the nitrogen atom and the quaternary carbon. The higher steric hindrance significantly lowered the yield of target sultams. In the presence of a phenyl substituent in the molecules, additional electron-withdrawing effect also decreased the efficiency of sulfonylation-cyclization sequence.

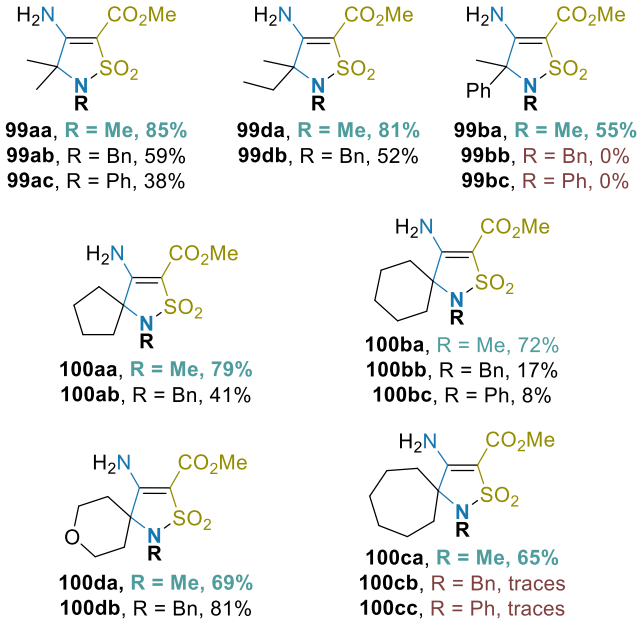


Figure 7. The influence of substituents on the yield of products **99** and **100**

The lowest yields of sultams were observed in the case of sulfonylation of *N*-phenyl-substituted aminonitriles for the synthesis of **99ac** (38% yield) and **100bc** (8% yield). In contrast, LCMS analysis revealed only trace amounts of products for the bulkiest cycloheptylidene-substituted derivatives **100cb** and **100cc**, which also contained *N*-benzyl and *N*-phenyl fragments, respectively. Prolonged reflux of the reaction mixture did not result in any observable reaction for *N*-benzyl-*C*-phenyl substituted aminonitrile **52bb**, as

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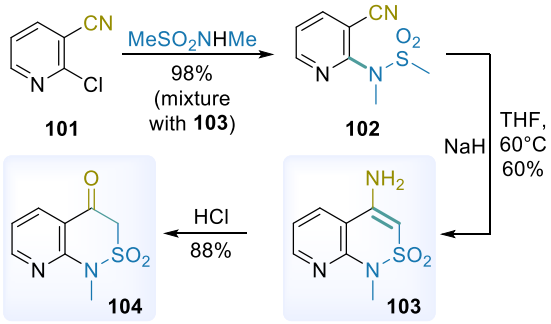
well as for derivative **52bc** with two phenyl substituents.

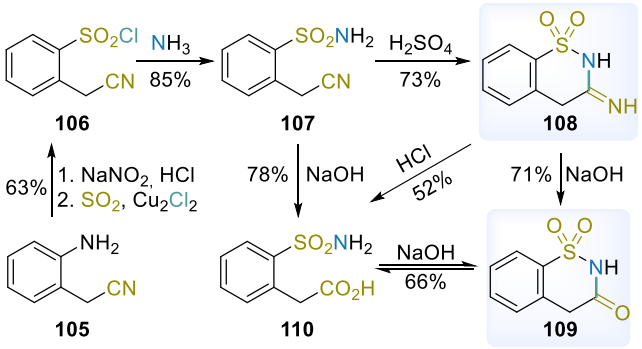
CSIC reactions are also employed for the construction of fused aromatic systems. For instance, *N*-arylation with 2-chloronicotinonitrile **101** of mesylated methylamine was utilized to obtain sulfonamide **102**. It is worth noting that upon the first step, a partial conversion of **102** into the cyclic product **103** of the CSIC reaction occurs. However, a complete conversion of **102** to **103** was achieved using NaH in THF, resulting in a 60% yield. Further acid hydrolysis of the enamine fragment led to the formation of ketosultam **104** (Scheme 13).[91]



Scheme 13. Synthesis of fused pyridosultams **1.66** and **1.67**

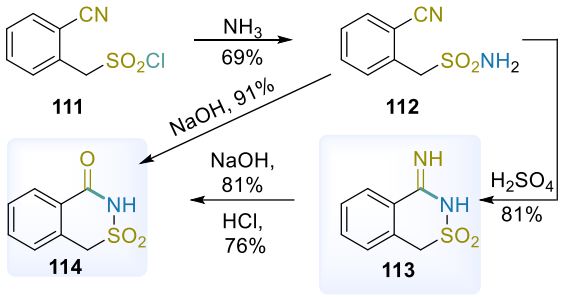
3.2 Synthesis of sultams using a sulfonamide group as a nucleophile in intramolecular condensation with phenyl and benzyl carbonitriles.

An example of the reactivity of sulfonamides as nucleophiles is the intramolecular reaction with a nitrile group as an electrophile. The key intermediates were obtained via the diazotization of aniline **105** for the preparation of sulfonyl chloride **106**, which is subsequently converted to sulfonamide **107** by the treatment with ammonia. When heated in concentrated sulfuric acid, compound **107** undergoes cyclization to form cyclic imidosulfonamide **108**, which can be further converted to amidosulfonamide **109** through alkaline hydrolysis. Both sultams **108** and **109** could be subjected to ring-opening reactions under acidic or basic conditions, respectively, which resulted in the formation of derivative **110** (Scheme 14).[92]



Scheme 14. Synthesis of 2*H*-benzo[*e*][1,2]thiazine-3(4*H*)-one-1,1-dioxide (**98**) and imidosulfonamide **109**

A similar approach is applied to the transformation of isomeric (2-cyanophenyl)methane sulfonyl chloride **111** to the corresponding sulfonamide **112**, which could be hydrolyzed to iminosultam **113** and ketosultam **114** (Scheme 15).[92]

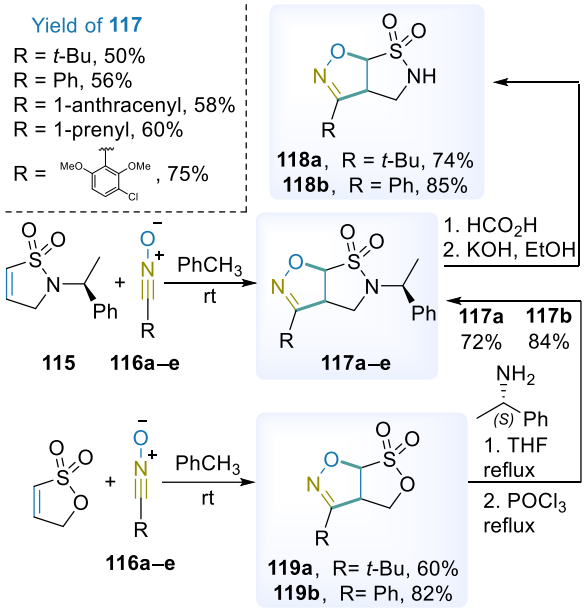


Scheme 15. Synthesis of 1*H*-benzo[*d*][1,2]thiazine-4(3*H*)-one-2,2-dioxide (**103**) and iminosulfonamide **104**

4. BOTH CARBON AND NITROGEN ATOMS OF THE NITRILE GROUP TO OCNSTRUCT THE SECOND RING OF FUSED SULTAMS

4.1 Synthesis of fused sultams by 1,3-dipolar [3+2] cycloaddition of nitrile oxides to unsaturated sultams

The α,β-unsaturated bond of the heterocycle acts as a 2π-component in 1,3-dipolar [3+2] cycloaddition reactions. For instance, sultam **115** reacts with nitrile oxides **116** via the 1,3-dipolar [3+2] cycloaddition to give the corresponding *cis*-fused bicyclic sultams **117a–e** (Scheme 16).[93]



Scheme 16. Cycloaddition of nitrile oxides **116** to sultam **115** and sultone for the synthesis of sultams **117**

The nitrogen atom of sultams could be protected with a phenylethyl group (removal with formic acid followed by the treatment with KOH). This approach allows for the synthesis of sultams **118a,b** with an unprotected amino group.

Furthermore, the products **119a,b**, formed as a result of 1,3-dipolar cycloaddition of nitrile oxides **116** to γ-sultone exhibit ability for the alkylatation reaction. These bicyclic sultones **119** could be converted into sultams **117a,b** through the action of (*S*)-(−)-α-methylbenzylamine, resulting in the formation of ammonium sulfonate salts that undergo cyclization with $POCl_3$.[94]

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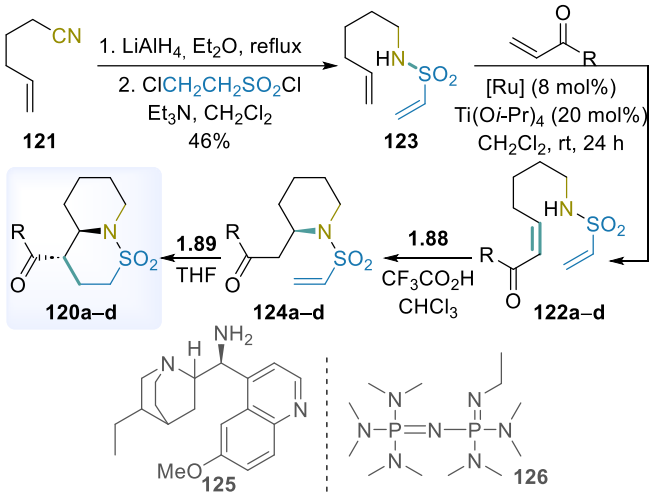
4.2. Cyclization via the key Michael addition

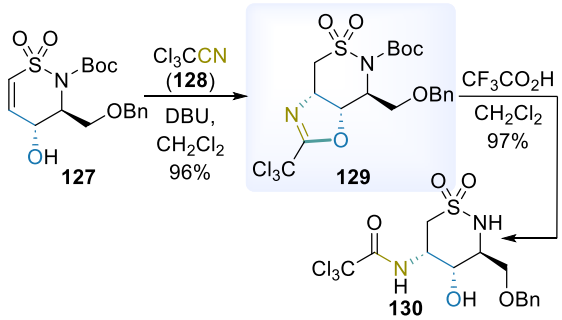
The Michael reaction, a nucleophilic addition to a conjugated unsaturated C=C bond, is also employed in the synthesis of sultams. An illustrative example is the enantioselective synthesis of bicyclic sultams **120** through a double consecutive Michael addition (Table 9).[95] The diatomic aminomethyl component for the construction of the future bicyclic sultam is provided by the nitrile group of hex-5-ene nitrile (**121**).

Table 9. Synthesis of bicyclic sultams **1.83** via the Michael reaction



N		R	Yield 122, %	Yield 124, %	*er*	Yield 120, %	*er*
1	**a**	Me	86	76	97:3	77	93:7
2	**b**	Pr	81	71	98:2	70	94:6
3	**c**	pentyl	70	90	98:2	73	95:5
4	**d**	Ph	45	65	98.5:1.5	80	90:10

The synthetic pathway involves reducing the nitrile fragment to the corresponding CH_2NH_2-substituent, which is then sulfonylated with 2-chloroethane sulfonyl chloride to introduce the vinyl sulfone fragment. The conjugated enones **122** are obtained through the cross-metathesis reaction of vinyl sulfonamide **123**. These enones **122** undergo an intramolecular asymmetric aza-Michael reaction with cyclization to form piperidines **124** by using quinine derivative **125** as a catalyst.



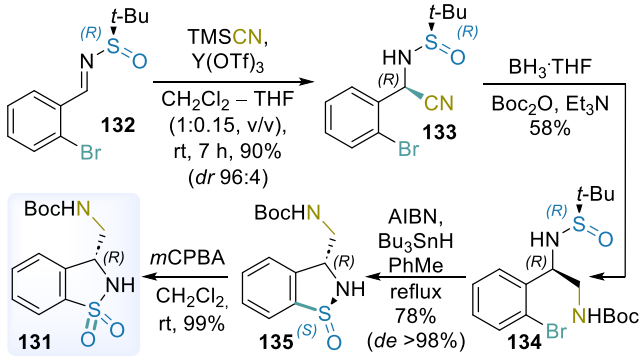
Scheme 17. Reaction of trichloroacetonitrile **128** for the synthesis of sultams **129** and **130**

Next, under the action of the sterically hindered base **126**, the methylene component of the derivatives is added as a *C*-nucleophile to the unsaturated vinyl sulfonamide bond by the second Michael reaction. This results in the formation of bicyclic δ-sultams **120**.

The nitrile group can also serve as a precursor of the amide fragment in the synthesis of bicyclic sultams. For instance, hydroxysultam **127** can react with trichloroacetonitrile **128** through the formation of imidate, followed by the intramolecular Michael addition to produce oxazoline **129**. The subsequent treatment of compound **129** with trifluoroacetic acid leads to the formation of acylated amino alcohol **130** (Scheme 17).[96]

4.3. Intramolecular homolytic substitution near the Sulfur atom.

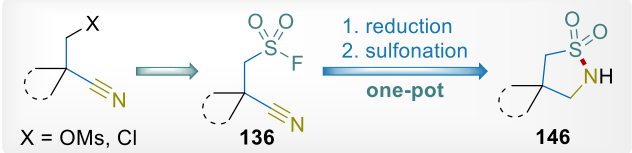
Another noteworthy advancement in the domain of assembling sultam heterocyclic fragments involves an intramolecular homolytic substitution reaction (S_Ni) near the sulfur atom. This method has been successfully employed to synthesize benzannelated γ-sultam **131** with a substituent at the C(3) position, achieving high enantiomeric purity. The synthetic transformation entails the addition of TMSCN to the double C=N bond of sulfinyl imine **132**, utilizing ytterbium triflate as a catalyst.[97] However, the resulting nitrile **133** was unsuitable for intramolecular homolytic substitution due to the preferential addition of *o*-aryl debrominated radical to the nitrile group rather than the sulfinamide group (**Scheme 18**). Consequently, to overcome this limitation, the nitrile group of compound **133** was converted into the *N*-Boc-protected aminomethyl-containing derivative **134**, which facilitates the subsequent formation of cyclic sulfinamide **135** with 78% yield and high diastereomeric excess (*de*) under the influence of AIBN and *n*-Bu_3SnH in toluene. Furthermore, the resulting sulfinamide **135** could be efficiently oxidized with mCPBA to produce sultam **131** in 99% yield.



Scheme 18. Cyclization through intramolecular homolytic substitution

5. REDUCTIVE CYCLIZATION OF CYANOALKANE SULFONYL FLUORIDES

A promising strategy for constructing spirocyclic scaffolds involves the intramolecular reductive cyclization reaction of 2-cyanoethane sulfonyl fluorides **136**, derived from monocyclic precursors (Scheme 19).[98]



Scheme 19. Synthesis of spirocyclic γ -sultams **146**

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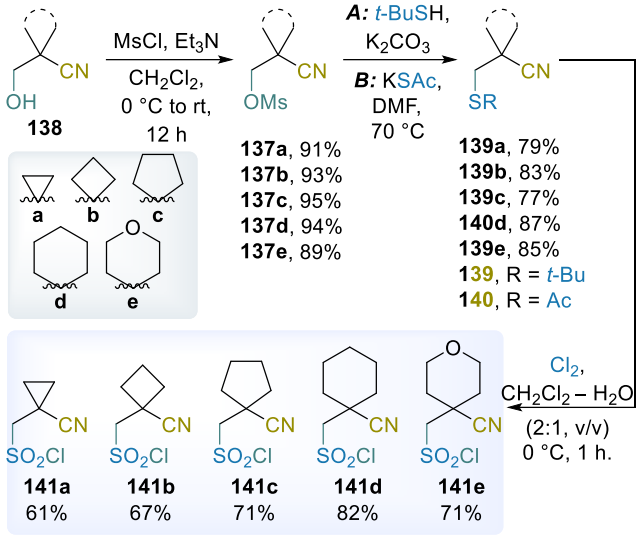
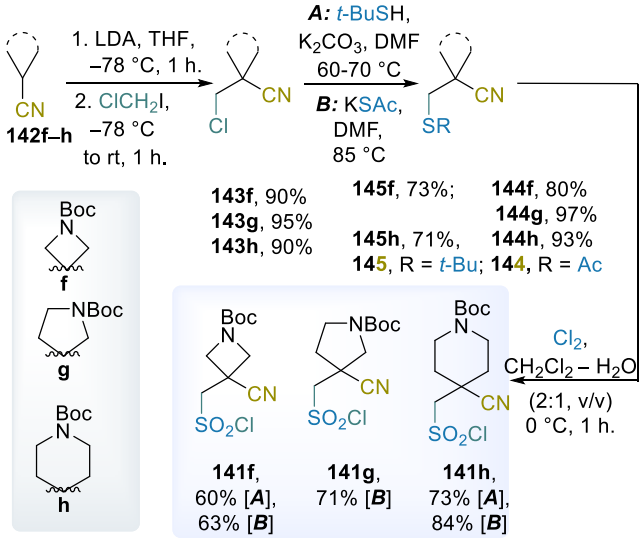
The reaction sequence relied on the preparation of mesylates **137a–e** (89–95% yield) from hydroxy nitriles **138** via mesylation in the presence of Et_3N in CH_2Cl_2. Subsequently, sulfur atom incorporation was achieved via nucleophilic substitution of **137** with *t*-BuSH in the presence of a base (Scheme 20). Most *tert*-butyl sulfides **139** were obtained with good yields, while better results were obtained in the case of using KSAc for cyclohexane derivative **139d** for the preparation of **140d**. Oxidative chlorination of *tert*-butyl sulfides **139a-c,e** and thioacetate **140d** was efficiently achieved using molecular chlorine (Cl_2) in a CH_2Cl_2–H_2O mixture (2:1, v/v), resulting in the formation of the corresponding β-cyanosulfonyl chlorides **141a-e** in 61–82% yield (Scheme 20).



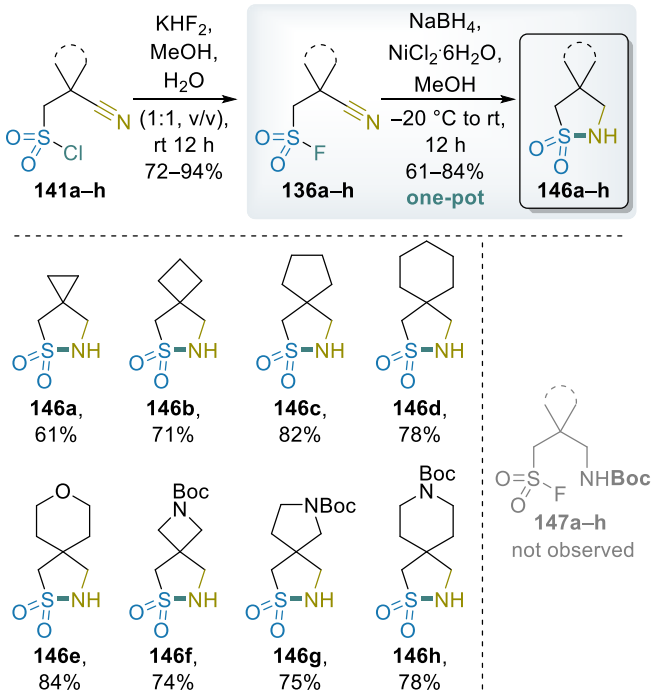
Scheme 20. Synthesis of sulfonyl chlorides **141a–e** with a cycloalkyl substituent

Moreover, the chloromethylation of *N*-Boc protected 3-cyanoazetidine **142f**, 3-cyanopyrrolidine **142g**, and 4-cyanopiperidine **142h** were accomplished by metallation of the compounds using LDA at –78 °C followed by alkylation with $ClCH_2I$, resulting in β-chloropropanenitriles **143f-h** (Scheme 21). Subsequent reactions with *S*-nucleophiles could be carried out as mentioned above for the case of carbocyclic derivatives.



Scheme 21. Synthesis of sulfonyl chlorides **141f–h** with an azaheterocyclic substituent

Due to the low stability of sulfonyl chlorides **141** under reducing conditions, they were transformed into the sulfonyl fluorides **136** by reaction with KHF_2 in MeOH–H_2O (1:1, v/v) at rt, and the corresponding SO_2F-substituted derivatives were synthesized in 72–94% yield (85% average). The key step involved the reduction of the nitrile group of SO_2F-substituted (hetero)cycloalkanecarbonitrile **136** with $NaBH_4$ in the presence of $NiCl_2{\cdot}6H_2O$ at –20°C. Remarkably, the iminoalkylsulfonyl fluorides formed initially underwent intramolecular sulfonylation and reduction, leading to the formation of the spirocyclic γ-sultams **146** in 61–84% yield after additional chromatographic purification (Scheme 22). Notably, even in the presence of Boc_2O, cyclization exclusively occurred to give sultams, while the formation of the corresponding aminoalkylsulfonyl fluorides **147** was not observed under the given synthesis conditions.



Scheme 22. Reductive sulfonylation for the synthesis of γ-sultams **146**

4.3. Reductive sulfonylation of α-cyanoalkylsulfonyl fluorides as a promising synthetic approach to β-sultams

The reductive cyclization is also efficient for the synthesis of lower homologs of **146**, e.g. spirocyclic β-sultams. The synthetic scheme involved the double alkylation of readily available 2-(*tert*-butylthio)acetonitrile **148** (Scheme 23). The reaction of **148** with NaH and 1,3-dibromopropane in DMF led to the formation of the cyclobutane derivative **149a** in 62% yield, while the use of 1-bromo-2-(2-bromomethoxy)ethane resulted in tetrahydropyranyl sulfide **149b** in 68% yield. The oxidative chlorination of **148** proceeded smoothly under typical conditions, providing the corresponding sulfonyl chlorides **150a** and **150b** in 80% and 87% product yields, respectively. Derivatives **150a** and **150b** were then converted to the corresponding sulfonyl fluorides **151a** (77% yield) and **151b** (66% yield), while the intramolecular reductive cyclization of which provided the corresponding β-sultams **152a** and **152b** under typical conditions, albeit with slightly lower yields (58% and 63%, respectively) compared to γ-analogs.[98]

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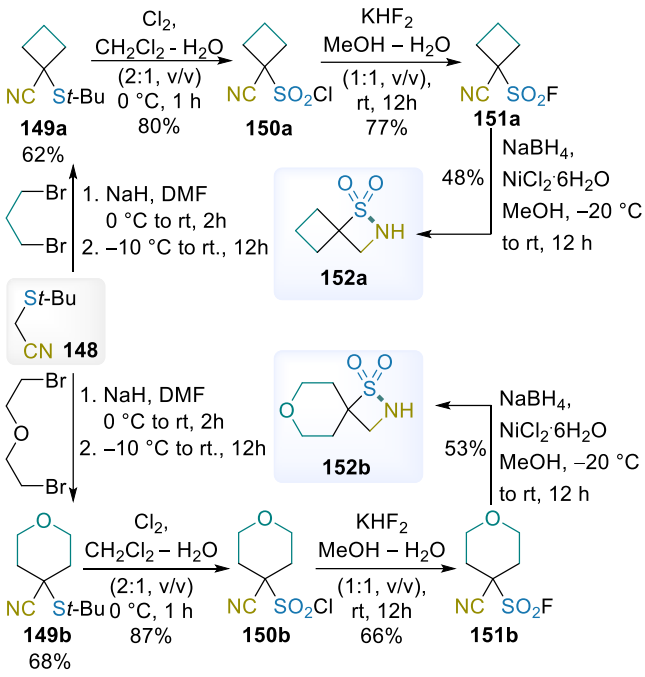
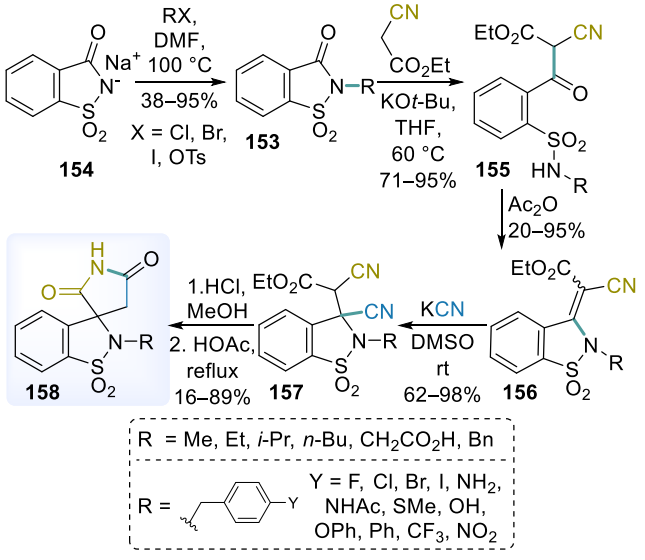


Scheme 23 . Synthesis β-sultams **152a** and **152b**

5. OTHER REACTIVITY OF NITRILES IN THE PREPARATION OF SULTAMS

Due to the acceptor properties of the nitrile group, the adjacent methylene unit becomes activated towards various condensation reactions. For instance, the reaction of ethyl-2-cyanoacetate with *N*-alkylsaccharins **153** (obtained from **154**) leads to the opening of the ketosultam fragment, resulting in the formation of sulfonamide **155** (Scheme 24).

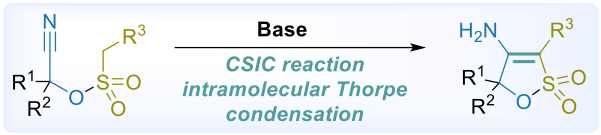


Scheme 24. Synthesis of spirosaccharins **158**

The subsequent recyclization of compound **155** occurs upon treatment with acetic anhydride, leading to the formation of the methylene sultam **156**. Further transformations involve the addition of the cyanide anion to the double C=C bond, resulting in the formation of dicyanoester **157**. This compound undergoes hydrolysis and decarboxylation reactions to give the spirocyclic succinimide **158**.[99] Throughout these transformations, the nitrile group exhibits desirable properties, including its electron-withdrawing nature, the presence of an electrophilic center, and nucleophilic reactivity.

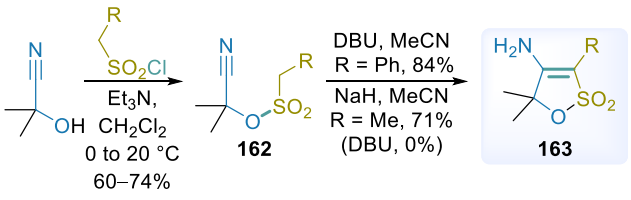
6. CSIC REACTION FOR THE CONSTRUCTION OF γ-SULTONE SKELETON

In contrast to the relatively wide scope of approaches for the preparation of sultams from nitriles, the liqst of known methods for the synthesis of sultones is significantly shorter. Notably, CSIC reaction is the most widely used approch for the synthesis of the γ-sultone fragment, similarly to the case γ-sultams,[61] and relied on the use of sulfonylated cyanohydrins (Scheme 25).



Scheme 25. CSIC reaction for the synthesis of sultones

To obtain 5,5-disubstituted sultones **159**, dialkyl- or cycloalkylidene cyanohydrins **160** were used.[86,100,101] The common sulfonylation with MsCl the presence of pyridine or Et_3N resulted the formation of sulfonates **161a**–**m** in 50–87% yield (Table 10). Further intramolecular cyclization in the presence of NaH in THF or MeCN resulted in the formation of the β-enamino-γ-sultone fragment **159**. It is shown that this method is suitable both for the synthesis of C-5 monoalkyl- and for obtaining 5,5-bisalkyl-substituted derivatives **159**. Monoalkyl-substituted cyanohydrins can also be used in sulfonylation reactions with homologous alkyl sulfonyl chlorides followed by carbanion cyclization.[102,103] The present method was studied with homologous sulfonylating agents, e.g. ethane sulfonyl chloride, and benzyl sulfonyl chloride (Scheme 26).[86] The cyclization reaction of sulfonates **162** into enaminosultones **163** proceeded smoothly by the use of DBU or NaH. Additionally, for certain substrates containing a benzyl substituent, Cs_2CO_3 in MeCN was found to be the preferred choice,[78,79] whereas the use of DBU led to E_2-elimination with the formation of substituted acrylonitrile.[79]



Scheme 26. Synthesis of 3-substituted enaminosultones **1.108** with acetone cyanohydrin

The scope of spirocyclic derivatives includes sultones, which were synthesized by sulfonylation of *N*-protected piperidine cyanohydrins **164** with methane-, ethane-, and benzyl sulfonyl chlorides upon the common conditions in the presence of Et_3N and CH_2Cl_2 to give sulfonates **165** in good yields ranging from 65% to 95%. Subsequently, these intermediates were subjected to CSIC reaction for the synthesis of spirocyclic analogs **166** using NaH or DBU as bases to provide enaminosultones in 69–91% yield (Scheme 27).[61]

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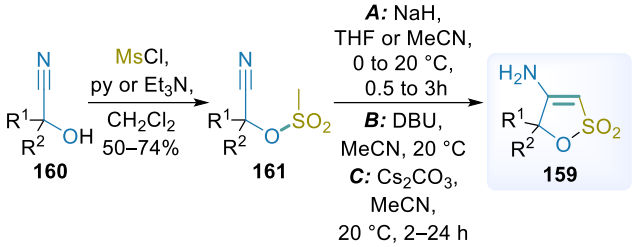
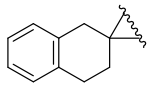
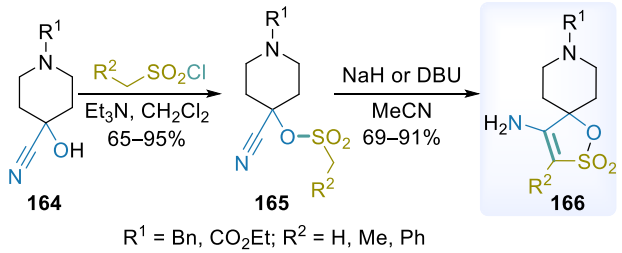
Table 10. Synthesis of sultones **159** from cyanohydrins

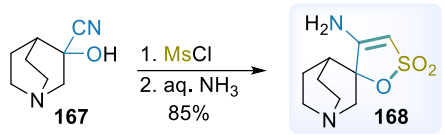


N	R^1	R^2	Yield 159, %		Method
1	Me	H	**159a**	50	***A***
2	Et	H	**159b**	61	***A***
3	Me	Me	**159c**	58–66	***A***
4				69	***B***
5	Me	Et	**159e**	84	***A***
6	Et	Et	**159d**	83	***A***
7				70	***C***
8	Et	Ph	**159e**	61	***A***
9	Bn	Me	**159f**	76	***A***
10				81	***C***
11	Bn	Pr	**159g**	50	***C***
12	Bn	*i*-Pr	**159h**	62	***C***
13	Bn	*s*-Bu	**159i**	66	***C***
14	Bn	Bn	**159j**	66	***C***
15	$CHPh_2$	Me	**159k**	76	***C***
16	Ph	CF_3	**159l**	62	***A***
17	CH_2 OTBDMS	CH_2CH_2 OTBDMS	**159m**	75	***C***
18	cyclopentyl		**159n**	91	***C***
19	cyclohexyl		**159o**	67	***A***
20			**159p**	70 [78]	***C***



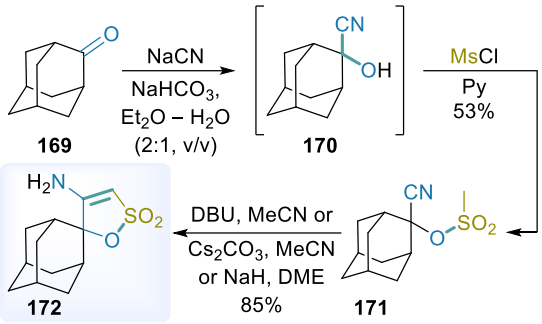
Scheme 27. Synthesis of azaspiroalkylidene-substituted sultones **166**

This synthetic strategy can be extended to bridged bicyclic cyanohydrins, enabling the synthesis of polycyclic alkylsultones. Specifically, 3-spiroquinuclidine **167** was obtained in 85% yield from the corresponding cyanohydrin **168** through mesylation followed by treatment with ammonia (Scheme 28).[104]



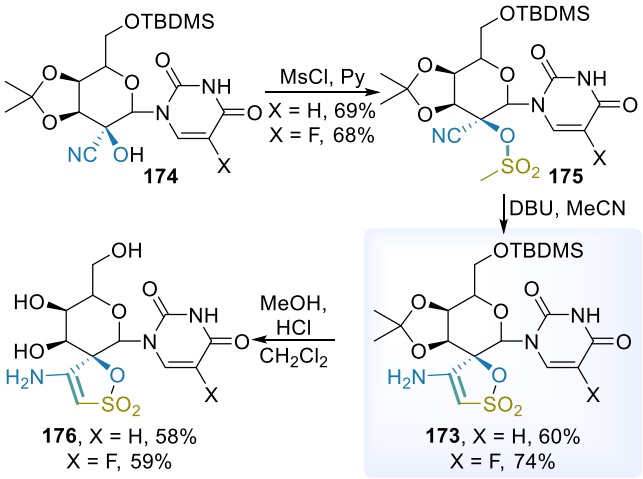
Scheme 28. Synthesis of 3,3-substituted spiroquinuclidine **1.112**

Furthermore, the transformation of adamantanone **169** into the corresponding cyanohydrin **170** was reported. Without isolation of **170** from the reaction mixture, it was subjected to mesylation-cyclization reactions, resulting in the formation of sulfonate **171** with a yield of 53% (Scheme 29). Subsequent cyclization under the action of any of the above-mentioned bases (DBU, NaH, Cs_2CO_3) with comparable efficiency led to the synthesis of spirocyclic 5,5-adamantyl sultone **172** in 85% yield.[105]



Scheme 29 . Synthesis of spiroadamantyl sultone **172**

In other studies, main efforts were focused on the synthesis of nucleoside spirosultams **173** from the corresponding cyanohydrins **174**. These were subjected to mesylation to form sulfonates **175** (68–69% yield), followed by intramolecular cyclization according to Thorpe to obtain sultones **173** (60–74% yield). Subsequently, *O*-desilylation was carried out to produce derivatives **176** (Scheme 30).



Scheme 30. Synthesis of nucleoside analogs **173** and **176**

Additionally, a synthetic route to isomeric compounds **177** and **178** was developed, following similar transformations of the corresponding derivatives **179** and **180** (Scheme 31).[106] As it was reported, 5-fluorouracil derivative could not be synthesized, while the sultone with a non-fluorinated uracil residue in the bridge was easily obtained in 70% yield.

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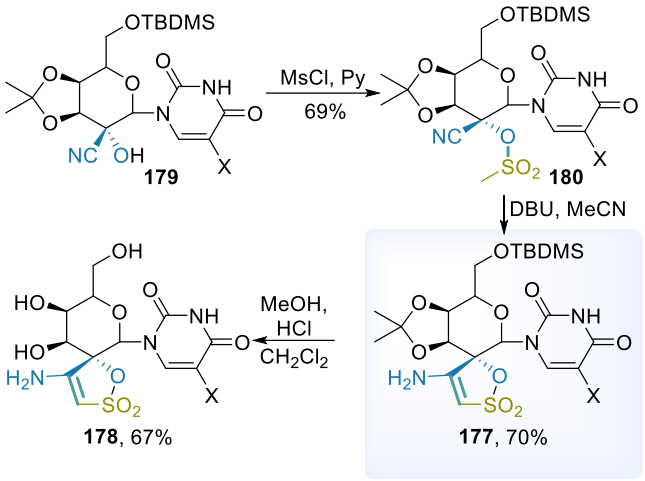
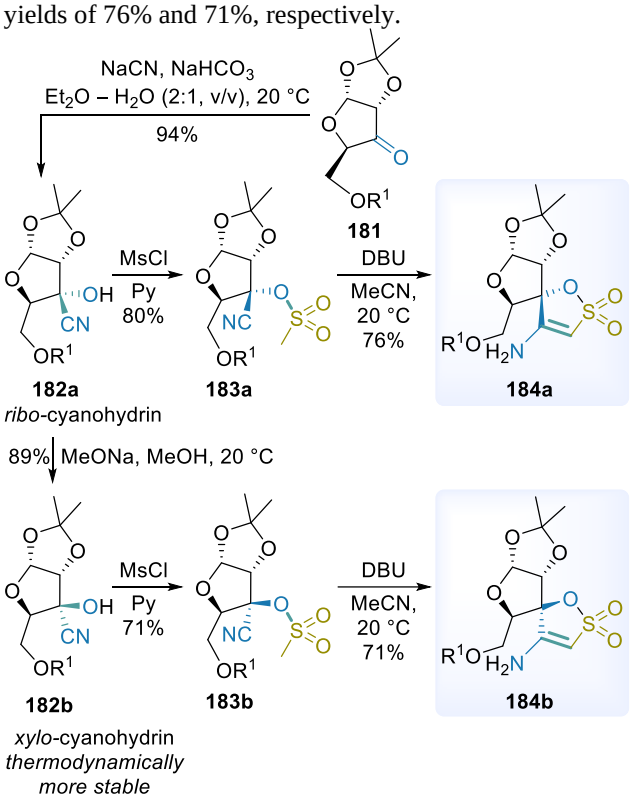


Scheme 31. Synthesis of enaminosultams **177** and **178**

Another interesting example included the use of ketone **181** for the preparation of the corresponding ribocyanohydrin **182a** in 94% yield, which could be epimerized to form the thermodynamically more stable xylocyanohydrin **182b** upon treatment with MeONa in MeOH in 89% yield (Scheme 32).[107] Subsequent mesylation of both stereoisomers **182a** and **182b** in pyridine led to the formation of sulfonates **183a** and **183b**, respectively, with yields of 80% and 71%. Further intramolecular cyclization of sulfonates **183a** and **183b** occurred upon treatment with DBU in MeCN, provideng sultones **184a** and **184b** with yields of 76% and 71%, respectively.

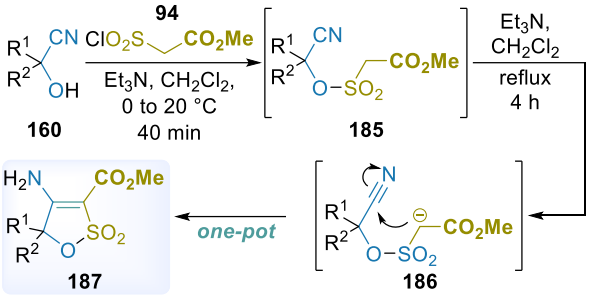


Scheme 32. Synthesis of stereoisomeric **184a** and **184b**

6.1 The use of cyanohydrins for the synthesis of γ -sultones-α -carboxylates

The scope of sp^3-enriched γ-sultones containing alkyl groups or a spirocyclic (hetero)cycloalkenylidene fragment was expanded by the method involving the simultaneous introduction of functional groups, such as α-alkoxycarbonyl or α-carbonitrile residues, along with the β-amino group of the enamine fragment.

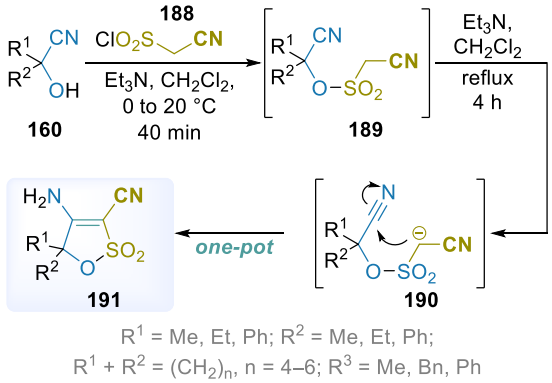
The sulfonylation of cyanohydrins **160** was carried out under conditions similar to those applied for aminonitriles **52** and **53** (Scheme 33).[108] In particular, Et_3N-catalyzed sulfonylation of the synthesized derivatives **185** was achieved by using of methyl-2-chlorosulfonyl acetate **94**, which resulted in the formation of cyanosulfonates **185**. The *C-H* acidity of the methylene unit in compounds **185** was sufficient for the deprotonation by triethamine, leading to the formation of carbanions **186**, which subsequently cyclized to form enaminosultones **187** (Figure 8). Notably, this method could be applied to monoalkyl-substituted cyanohydrin for the preparation of **187j** (45% yield).



Scheme 33. One-pot synthesis of sp^3-enriched sultones **187** modified with hetero(cyclo)alkyl substituents

6.2 Use of cyanohydrins for the synthesis of γ-sultone-α-carbonitrile

The proposed method was further extended to utilize cyanomethane sulfonyl chloride **188** for the synthesis of nitrile-substituted γ-sultones (**Scheme 34**). This transformation proceeded smoothly under similar conditions to sulfonylation with chlorosulfonyl acetate **94**, generating sulfonates **189** and the corresponding carbanions **190** in a one-pot mode.



Scheme 34. Synthetic approach to γ-sultone-α-carbonitrile **191**

This synthetic approach led to the formation of γ-sultone α-carbonitrile **191** with yields ranging from 30% to 56% (Figure 8). The yields were comparatively lower in contrast to similar experiments with sulfonyl chloride **94**, primarily due to the relatively lower stability of sulfonyl chloride **188** bearing nitrile moiety under reaction and storage conditions.

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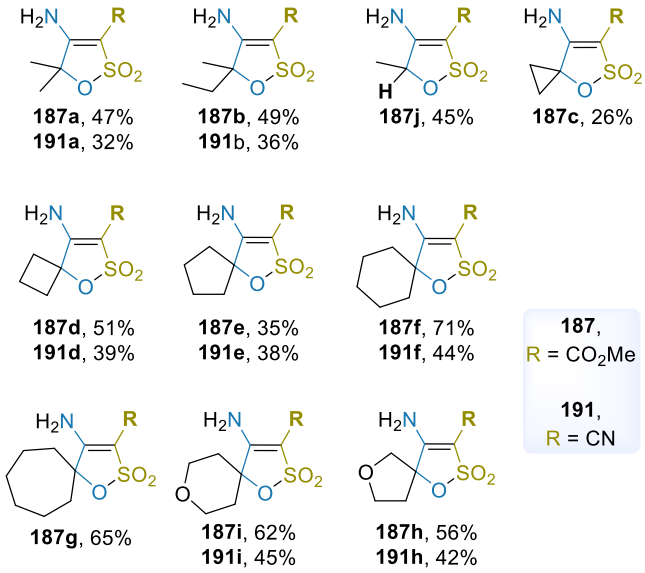
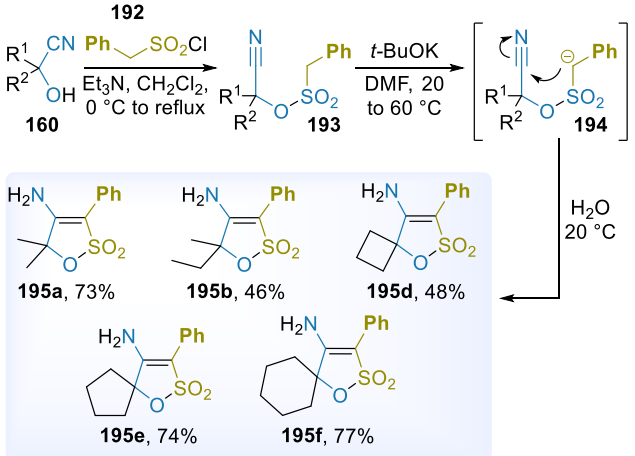


Figure 8. Percentage yields of synthesized sultone carboxylates **187** and nitriles **191**

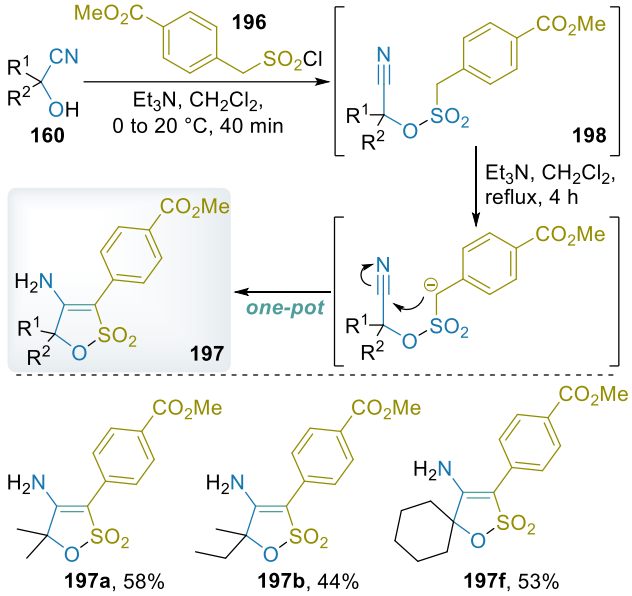
6.3 Reactions of arylmethane sulfonyl chlorides and cyanohydrins for the synthesis of α-aryl-β-enamino-γ-sultones

The scope and limitations of one-pot sulfonylation-cyclization reactions is limited to highly active methylene unit. This was demonstrated by reactions with phenylmethane sulfonyl chloride **192** with cyanohydrins under the common conditions, which resulted in the formation of corresponding cyanosulfonates **193** (Scheme 35), while the subsequent cyclization required the use of stronger base *t*-BuOK in DMF to initiate the CSIC reaction. Therefore, α-phenyl-β-enamino-γ-sultones **195** could be obtained only using the two-step approach in good yields up to 77%.[109]



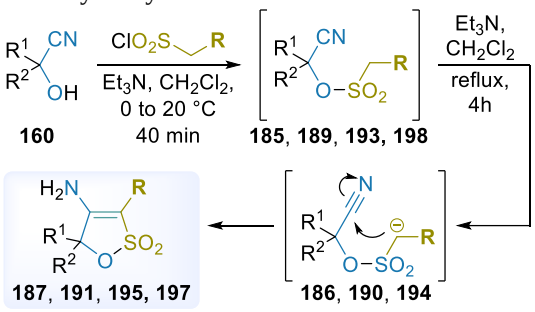
Scheme 35. Two-stgep synthesis of α-phenyl-β-enamino- γ -sultones **195** via intermediate sulfonates **193**

In turn, the introduction of an electron-withdrawing group into the aromatic substituent of phenylmethane sulfonyl chloride could facilitate the cyclization of *O*-sulfonylated cyanohydrins and enable a one-pot CSIC reaction. The use of (4-carbomethoxyphenyl)methane sulfonyl chloride **196** as a sulfonylating agent in the reaction with cyanohydrins **184** provided the corresponding enaminosultones **197** in moderate yields according to the common method (Scheme 36, Table 11).



Scheme 36. One-pot synthesis of sultones **197** from methyl-4-((chlorosulfonyl) methyl)benzoate **196**

Table 11. The scope of one-pot sulfonylation and CSIC reaction of cyanohydrins



N	R^1	R^2	R	Product	Yield, %
1	Me	Me	CO_2Me	**187a**	47
2	Me	Et	CO_2Me	**187b**	49
3	$(CH_2)_3$		CO_2Me	**187c**	51
4	$(CH_2)_4$		CO_2Me	**187d**	35
5	$(CH_2)_5$		CO_2Me	**187e**	71
6	$CH_2O(CH_2)_2$		CO_2Me	**187f**	56
7	$(CH_2)_2O(CH_2)_2$		CO_2Me	**187g**	62
8	H	Me	CO_2Me	**187h**	45
9	Me	Me	CN	**191a**	32
10	Me	Et	CN	**191b**	36
11	$(CH_2)_3$		CN	**191c**	39
12	$(CH_2)_4$		CN	**191d**	38
13	$(CH_2)_5$		CN	**191e**	44
14	$CH_2O(CH_2)_2$		CN	**191f**	42
15	$(CH_2)_2O(CH_2)_2$		CN	**191g**	45
16	Me	Me	*p*-CO_2Me-C_6H_4	**197a**	58
17	Me	Et	*p*-CO_2Me-C_6H_4	**197b**	44
18	$(CH_2)_5$		*p*-CO_2Me-C_6H_4	**197f**	53

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7. CONCLUSIONS

The cyano group has proven to be a versatile and valuable building block in the synthesis of sultams. It can directly participate in the formation of the sultam skeleton or serve as an activator for adjacent positions. The most common transformation involving the nitrile group is the CSIC reaction, where the nitrile acts as an electrophilic center for attack by a carbanion, leading to the formation of enamines and subsequent cyclization. Additionally, the nitrile's acceptor properties enable the introduction of substituents into α-positions through alkylation or cyclization reactions. The acceptability of nitriles is crucial for activating unsaturated bonds in various [3 + 2] and [4 + 2] cycloadditions, as well as in 1,3-dipolar cycloaddition reactions with nitrile oxides to form fused sultam derivatives.

Based on the literature review, it has been established that utilizing the nitrile group as a precursor of the methyleneamine component holds great promise for further research in sultam synthesis. Therefore, it is of interest and significance to explore the applicability of this method for the synthesis of spirocyclic sultams, where the nitrile group serves as a diatomic CN component in the formation of future heterocyclic systems. This approach opens up new avenues for the efficient synthesis of functionalized spirocyclic sultams with potential applications in various fields of chemistry and biology.

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