SECTION 10.
CHEMISTRY, CHEMICAL ENGINEERING AND BIOENGINEERING

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SULTONES – PERSPECTIVE SUBSTANCES IN ORGANIC SYNTHESIS

One of the most important tools of modern pharmaceutical and medical chemistry is replacement with a bioisosteric fragment, which can lead to increased activity, selectivity and metabolic stability of drugs, as well as improve their pharmacokinetic and pharmacodynamic properties.

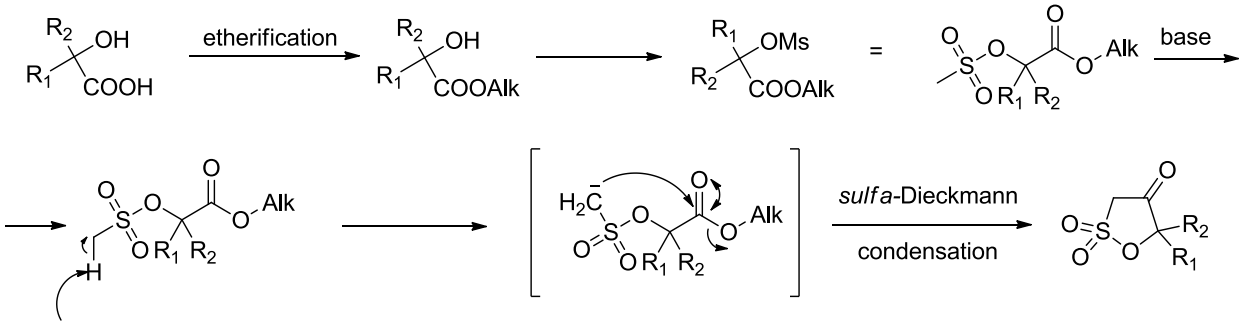
1,2λ^6-oxathiolane – 2,2,4 – triones belong to the class of cyclic sulfonates (sultones) and are considered as sulfur-containing bioisosteres of tetronic acid (oxolane-2,4-dione). Derivatives of tetronic acid are widespread in nature and have a wide range of biological activity: powerful antibiotic effect, antiviral and antiulcer properties, cytotoxic, and fungicidal activity, suppress tumor growth, etc.

Most of the low-molecular-weight compounds used in the production of drugs have rigid structure that reduce entropy losses when binding to the target. Rigid structural elements include, among others, small rings and spirocyclic systems. Another important criterion for the use of substances in medical practice is resistance to metabolism. In this regard, spirocyclic compounds possessing quaternary carbon atoms are resistant to metabolic attacks and therefore have attracted considerable attention [1].

To date, despite their diverse biological activity, synthetic and pharmaceutical potential, β-keto-γ-sultones have been insufficiently studied. Therefore, the development of methods for the synthesis of 5,5-disubstituted and spirocyclic 1,2λ^6-oxathiolane-2,2,4-triones as well as their further modification with the aim of introducing pharmacophore groups, linkers, and other functional handles is an important task of modern organic chemistry. These findings would stimulate the discovery of novel biologically active substances and pharmaceuticals creation.

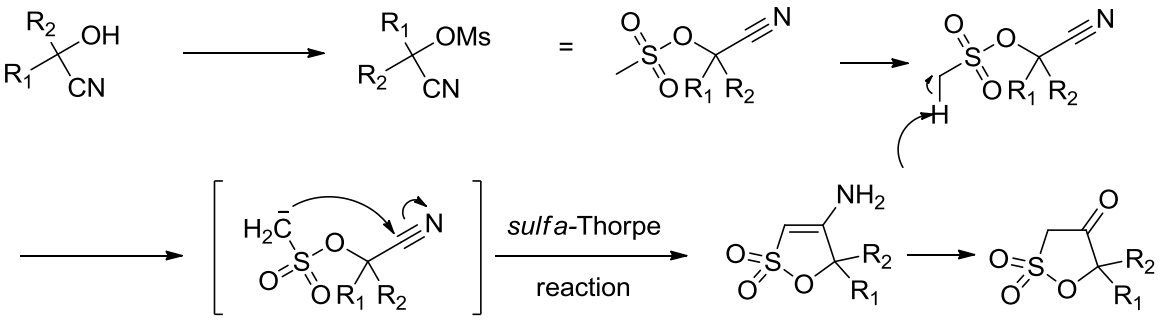
One of the most applicable methods for the synthesis of 5,5-disubstituted sultones is the CSIC reaction (Carbanion-mediated Sulfonate (or Sulfonamide) Intermolecular Coupling, and Intramolecular Cyclization). This easy to handle reaction has a wide substrate scope and based on the *sulfa*-Dieckmann or *sulfa*-Thorpe reaction. The starting materials for the conversion are oxyesters or cyanohydrins, which can be obtained quite easily from commercially available ketones.

The first step is the mesylation of the hydroxyl group of the oxyester or cyanohydrin. Next, the methyl fragment of mesyl is deprotonated in the presence of a base (for example, potassium *tert*-butylate or sodium hydride) with the formation of an anion. In the next step, the anion attacks the carboxylate or nitrile group, eventually affording cyclic sulfonate – sultone (Scheme 1, 2) [2,3].



$R_1 = R_2 = Alk$
$R_1 + R_2 = c\text{-Alk}$, Het etc.

Scheme 1



$R_1 = R_2 = Alk$
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Scheme 2

The treatment of β-keto-γ-sultones with DMF-DMA led to valuable synthetic precursors (Scheme 3). The adjacent carbonyl and dimethylaminomethylidene groups are considered as hidden 1,3-dicarbonyl functionality, applicable for constructing the fused heterocyclic systems.

Scheme 3

References:

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2. Dobrydnev, A. V., & Marco-Contelles, J. (2021). Eur. J. Org. Chem. , 1229-1248.
3. Dobrydnev, A. V., Vashchenko, B. V., & Yulian, V. M. (2018). Tetrahedron Lett. , 59, 1581-1582.