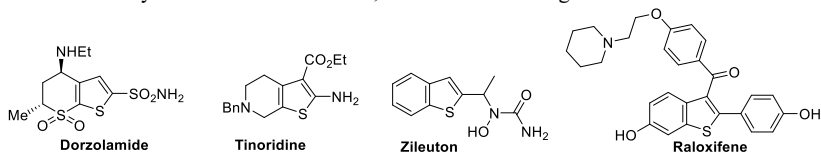


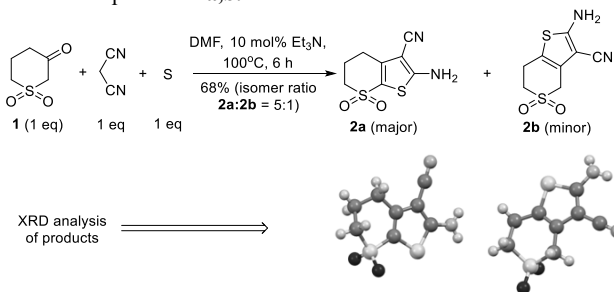
DIHYDRO-2H-THIOPYRAN-3(4H)-ONE 1,1-DIOXIDE IN GEWALD'S CHEMISTRY

Shevchenko O. V.¹, Shishkina S. V.², Palchykov V. A.¹¹Oles Honchar Dnipro National University
49010, Dnipro, Gagarina Str. 72, Ukraine²Institute for Single Crystals, 61072, Kharkiv, Nauky Av. 60, Ukraine
tigra8olchik@gmail.com

Since 1961, when the first report on the Gewald reaction was published, it has become a universal method for synthesis of substituted 2-aminothiophenes and has gained prominence in recent times. The availability of reagents and the mild reaction conditions all contribute to the versatility of this reaction. Among the best-known examples of commercially available drugs that contain a thiophene ring as pharmacophoric group antiglaucoma agent Dorzolamide, anti-inflammatory Tinoridine and Zileuton, and anti-cancer drug Raloxifene.



As a rule, symmetrical ketones are used in Gewald reaction to avoid obtaining a mixture of regioisomeric products. Our interest in dihydro-2H-thiopyran-3(4H)-one-1,1-dioxide **1** has arisen due to its high reactivity in multi-component reactions (MCR) and wide applicability in the synthesis of various bioactive heterocycles. Our preliminary screening of the reaction conditions indicated that a 5:1 mixture of isomers was formed. We succeeded in separating this mixture by fractional recrystallization from a MeCN/*i*-PrOH solution and obtained X-ray diffraction data for both products **2a,b**.



Recently, improvements to the Gewald synthesis have been discovered based on a reduction in reaction time using microwave technology. Thus, we plan to further optimize our reaction to increase its regioselectivity. It is also proposed to use selenium instead of sulfur as a method for obtaining new Se-containing heterocycles. Malononitrile will also be replaced with similar components (methyl and ethyl cyanoacetates, 2-cyanoacetamide, 3-oxo-3-phenylpropanenitrile) to produce a series of new Gewald products.

In addition, we have screened *in silico* biological profile of new thiophenes **2a,b** using free online tool <https://www.molpredictx.ufpb.br> (Laboratory of Cheminformatics, Federal University of Paraíba, Brazil). The prediction suggests high (60 % and higher) probability levels of activity against *Sars-Cov*, *Dengue Larvicida*, *Candida Albicans* and *Tripomastigote Chagas* species for compound **2a**, and high probability levels of activity against *Dengue Larvicida*, *Alphis gossypii*, *Tripomastigote Chagas* species for compound **2b**. Thiophene **2b** is also predicted to exhibit anti-Alzheimer's activity.