

Sēra dioksīda izmantošana augstas pievienotās vērtības produktu sintēzē



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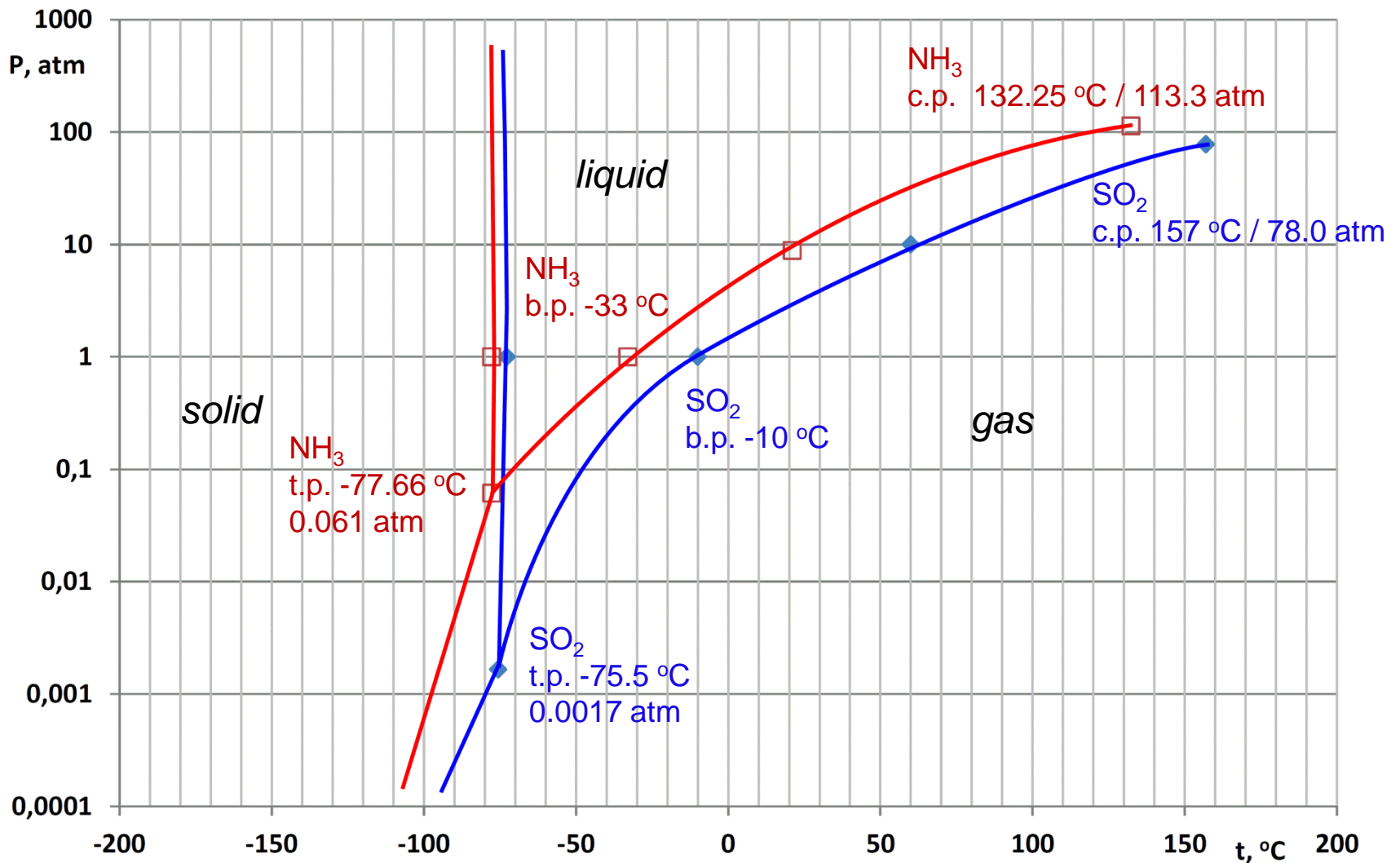
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[*École polytechnique fédérale de Lausanne*]

Latvijas Zinātnes padomes grants 291/2012



SO₂ un NH₃ fāzu stavokļu diagrammu salīdzinājums

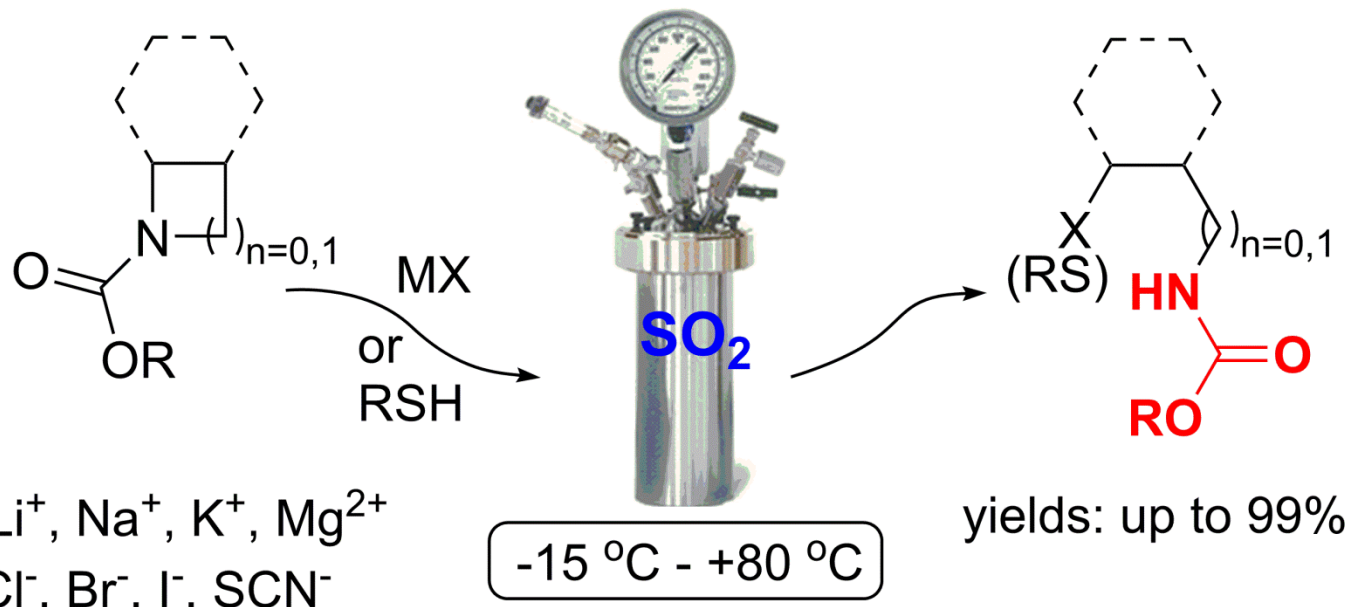




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Sēra dioksīda izmantošana augstas pievienotās vērtības produktu sintēzē

Atklājām, ka šķidrums sēra dioksīds kā polārs un Luisa skābs šķīdinātājs aktivē gan ar karbamātu grupām aizsargātus, gan neaizsargātus (NH-forma) aziridīnus un azetidīnus to cikla uzšķelšanas reakcijās ar halogēnīdiem, pseidohalogēnīdiem un tioliem. Izstrādātās metodes ir vienkāršas, un pēc SO_2 kā šķīdinātāja reciklējošās attvaicēšanas, produkti tiek iegūti praktiski tīrā veidā.



Jevgeņija Lugiņina





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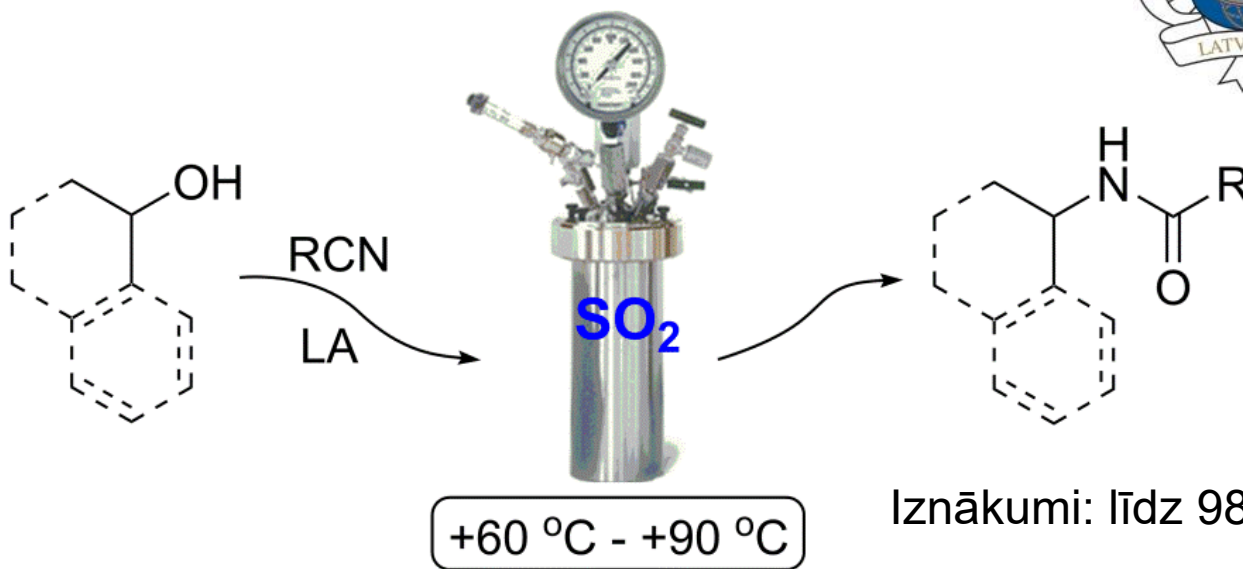
Sēra dioksīda izmantošana augstas pievienotās vērtības produktu sintēzē

Atklāts, ka šķidra SO_2 Luisa skābās un jonizējošās īpašības ir izcili piemērotas reakcijām, kuru intermediāti ir karbēnija joni. Mūsu izstrādātais protokols dod līdz šim labākos zināmos rezultātus šādu neaktivētu spirtu Ritera reakcijām katalītiskos apstākļos.

Izstrādātie apstākļi piemēroti tādu ārstniecības vielu kā amantadīna un memantīna sintēzē un aromatizētāja mentilamīna sintēzē



Daniels Posevins
LZA balva par maģistra darbu



Krista Suta

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Projekta gaitā tika izstrādāta jauna reaģentu klase – trialkilsilil-alilsulfināti, kuri sevi pierādīja kā izcili sililgrupas pārnesoši reaģenti.

Tādejādi tie ir piemērojami dažādu tipu HO-grupu sililēšanai gan sintētiskos nolūkos, gan ar pielietojumu kā kvantitatīvi atvasināšanas reaģenti grūti gaistošu un termiski nestabilu savienojumu gāzu hromatogrāfiskajā analīzē.

Reprezentatīva grūti gaistošu vielu GC-MS analīze

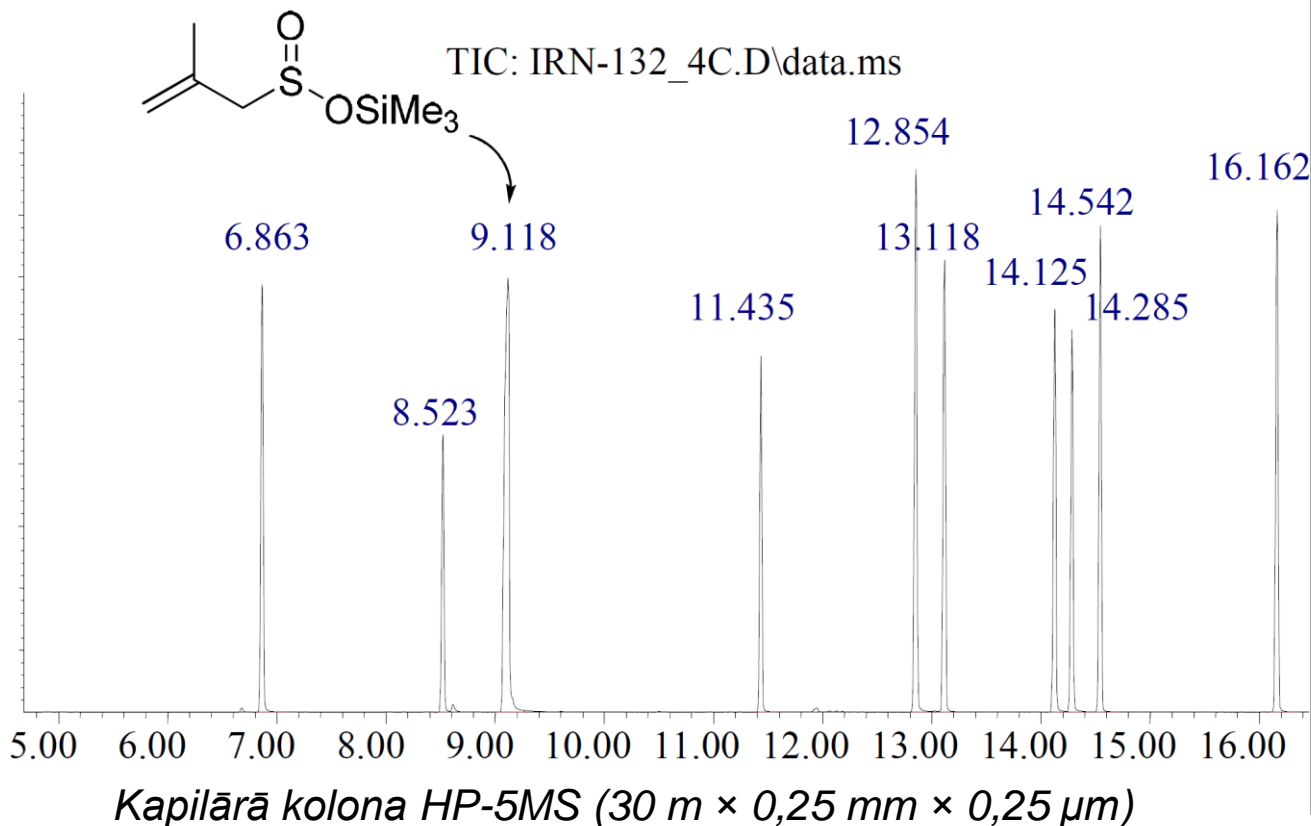
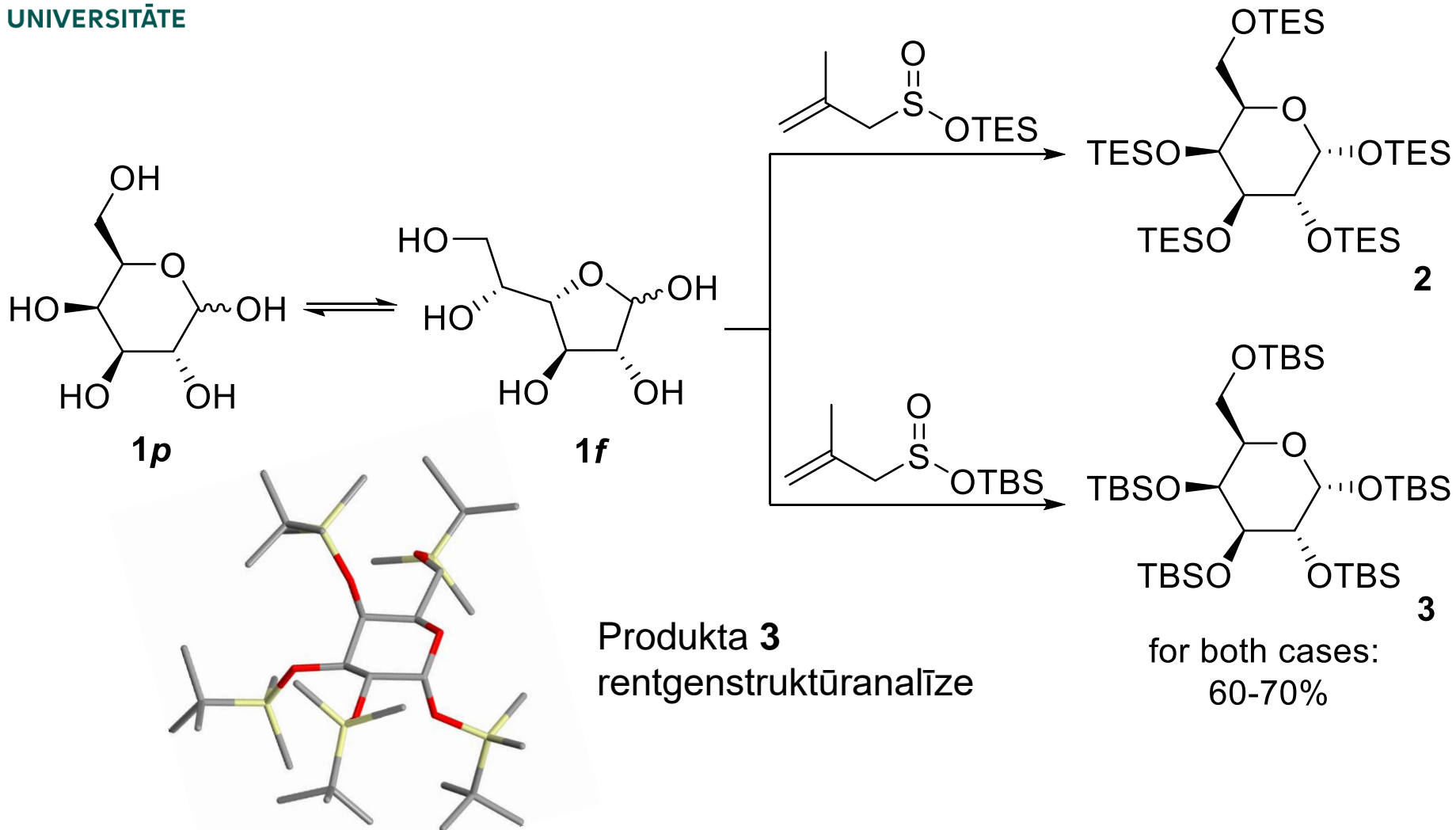


Table. Retention times of O-silylated polyhydroxy compounds depicted in GC-MS traces.		
Entry	Retention time, min.	Silyl derivative
1	6.86	<chem>TMSOCCOTMS</chem>
2	8.52	<chem>TMSOCC(C)(C)COTMS</chem>
3	11.44	<chem>TMSOCC(C)C(C)COTMS</chem>
4	12.85	<chem>TMSOc1ccc(OTMS)cc1</chem>
5	13.12	<chem>TMSOCC(C)(C)C(C)COTMS</chem>
6	14.13	<chem>CC(=O)C(O)C1=CC=CC=C1</chem>
7	14.29	<chem>CC(=O)C(O)C(C)C(=O)C</chem>
8	14.54	<chem>TMSOCC(C)(C)C(C)COTMS</chem>
9	16.16	<chem>CC(=O)C(O)C(C)C(=O)C</chem>

Galaktozes sililēšana



Līdz šim bija iespējams iegūt tikai galaktofuranozes formas, lietojot sililēšanas metodi:

J. Org. Chem. **2012**, *77*, 1301; *J. Org. Chem.* **2009**, *74*, 1994



Irina Novosjolova



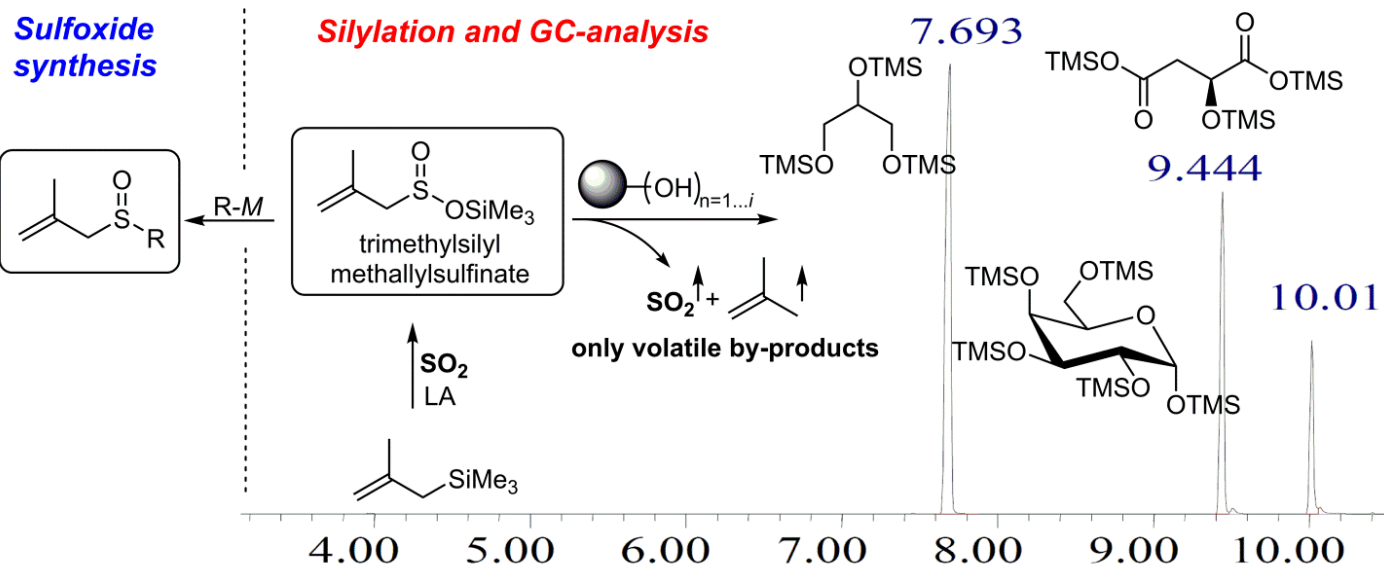
Agnese Stikute



LZA balva par maģistra darbu

Sulfoxide synthesis

Silylation and GC-analysis

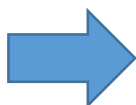


Jaunatklātie sili-sulfināti kā vielu klase, kas iegūta no sēra dioksīda, ir pielietojami gan kvalitatīvajā un kvantitatīvajā gāzu hromatogrāfijā, gan preparatīvajā sili-lēšanā, gan kā reaģenti sulfoksīdu sintēzē.

Praktiskais izpildījums reakcijām šķidrā sēra dioksīdā temperatūrās virs $-10\text{ }^{\circ}\text{C}$ *Pilnīga šķīdinātāja reciklēšanas iespēja*



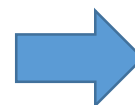
Reaktors ar
izejvielām



SO_2 kondensēšana
reaktorā no
uzglabāšanas trauka



Reakcija



SO_2 pārnese atpakaļ uz
uzglabāšanas trauku



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Publikācijas un patenti par pētījuma tēmu

SCI Publikācijas (SCOPUS un Web of Science)

- 1) Lugiņina, J.; Turks, M. Regioselective Ring Opening of *N*-H-Aziridines with Sulfur Nucleophiles in Liquid SO₂. *Synlett* **2017**, in press. 10.1055/s-0036-1588670
- 2) Posevins, D.; Suta, K.; Turks, M. Indium-Triflate-Catalyzed Ritter Reaction in Liquid Sulfur Dioxide. *Eur. J. Org. Chem.* **2016**, 1414–1419.
- 3) Lugiņina, J.; Uzuleņa, J.; Posevins, D.; Turks, M. A ring-opening of carbamate-protected aziridines and azetidines in liquid sulfur dioxide. *Eur. J. Org. Chem.* **2016**, 1760–1771.
- 4) Marković, D.; Tchawou, W. A.; Novosjolova, I.; Laclef, S.; Stepanovs, D.; Turks, M.; Vogel, P. Synthesis and Applications of Silyl 2-Methylprop-2-ene-1-sulfonates in Preparative Silylations and GC Derivatizations of Polyols and Carbohydrates. *Chem. Eur. J.* **2016**, 22, 4196–4205.
- 5) Stikute, A.; Peipiņš, V.; Turks, M. Synthesis of allyl sulfoxides from allylsilanes via silyl sulfonates. *Tetrahedron Lett.* **2015**, 56, 4578-4581.
- 6) Novosjolova, I.; Turks, M. User friendly synthesis of Vogel's silyl sulfonate and its application in quantitative GC-MS analysis. *Phosphorus, Sulfur Silicon Rel. Elem.* **2015**, 190, 1251-1256.
- 7) Stepanovs, D.; Posevins, D.; Turks, M. Crystal structures of two (±)-exo-*N*-isobornylacetamides. *Acta Crystallogr. Sect. E.* **2015**, 71, 1117-1120.
- 8) Lugiņina, J. Sulfur Dioxide in the Past Decade. *Synlett* **2014**, 25, 2962-2963.

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- 1) Stikute, A.; Turks, M. Sulfonu sintēzes paņēmieni no kālija aliltrifluorborātiem. Latvijas patenta pieteikums LV15139A, 22.04.2016.
- 2) Turks, M.; Posevins, D.; Rjabovs, V. Amīdu sintēzes paņēmieni Ritera reakcijā šķidrā sēra dioksīdā. Latvijas patents LV15095B, 20.03.2016.
- 3) Turks, M.; Lugiņina, J.; Rjabovs, V. Azetidīnu cikla uzslēgšanas paņēmieni ar nukleofiliem šķidrā sēra dioksīdā. Latvijas patents LV15096B, 20.03.2016.
- 4) Lugiņina, J.; M. Turks. Annelētu aziridīnu cikla uzslēgšanas paņēmieni ar nukleofiliem šķidrā sēra dioksīdā. Latvijas Patents LV14955B, 20.04.2015.
- 5) Stikute, A.; Novosjolova, I.; Turks, M. Sulfoksīdu sintēzes paņēmieni no trialkilsililsulfonātiem. Latvijas Patents LV14981B, 20.06.2015.
- 6) Lugiņina, J.; Rjabovs, V.; Turks, M.; Mackeviča, J. 2-Amino-3-halogēn-karbonskābju atvasinājumu un 2-amino-3-pseidohalogēn-karbonskābju atvasinājumu iegūšanas paņēmieni. 14778 B, 20.03.2014.

Wiley izdevniecības grāmatas nodaļa:

Vogel, P.; Markovic, D.; Turks, M. Sulfur dioxide: a powerful tool for the stereoselective construction of C-C bonds. In: *Stereoselective synthesis of drugs and natural products*. Andrushko, V.; Andrushko, N., Eds. Wiley-Blackwell, 2013, pp.623-666.



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ChemPubSoc Europe DOI: 10.1002/chem.201504380

Synthetic Methods

Synthesis and Applications of Silyl 2-Methylprop-2-ene-1-sulfonates in Preparative Silylation and Reactions of Polyols and Carbohydrate

Dean Marković,^[a] Wandji Augustin Tchawou,^[a] Irina Dmitrijs Stepanovs,^[a] Māris Turks,^[a] and Pierre Vogel

Abstract: Trimethylsilyl, triethylsilyl, tert-butyl dimethylsilyl, and triisopropylsilyl 2-methylprop-2-ene-1-sulfonates were prepared through Cu(OTf)₂-C₄H₉-catalyzed silyl-ene reactions of the corresponding methylsilanes with SO₂ at 50 °C. Sterically hindered, epimerizable, and base-sensitive alcohols gave the corresponding silyl ethers in high yields and purities at room temperature and under neutral conditions. As the byproducts of the silylation reaction (SO₂ + isobutylene) are volatile, the workup was simplified to solvent evaporation. The developed method can be employed for the

Introduction

The selective silylation of polyols, phenols, carboxylic acids, and other compounds containing hydroxy groups is of great importance in modern organic synthesis.^[1] Silyl ethers and derivatives^[2] are recognized as the most valuable protect-

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Synthesis of allyl sulfonides from allylsilanes via silyl sulfonates

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ABSTRACT

Allylsilanes underwent silyl-ene reaction with sulfur dioxide in the presence of Lewis acid catalysts. The obtained Vogel's silyl sulfonates were found to act as sulfanyl transfer agents in reactions with aryl, heteroaryl, alkyl, and allyl Grignard reagents proceeding with the expulsion of the trialkylsilyloxy group to give allyl sulfonides in up to 83% yield. The nucleophilic attack of Grignard reagents was accelerated in toluene and in the presence of LiCl or ZnCl₂ as Lewis acidic additives. The developed method allows the transformation of allylsilanes into allyl sulfonides.

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Synlett J. Luginja, M. Turks Letter

Regioselective Ring Opening of N-H-Aziridines with Sulfur Nucleophiles in Liquid SO₂

Chemistry, Faculty of Science, Federal Institute of Technology, Lausanne, CH-1015, Lausanne

Introduction

Carbamate-protected aziridines and azetidines in liquid sulfur dioxide as solvent resulted in the efficient ring-opening of these heterocycles. Sulfur dioxide, as a highly polar solvent, solubilizes the inorganic salts and acts as a Lewis acid to accelerate the ring-opening. For this reason, carbamate-protected small heterocycles can be used instead of the corresponding sulfonamides, the activities of which are well-established in ring-opening reactions. This also performed well in the SO₂-assisted ring-opening of aziridines. This procedure occurred without racemization of the stereogenic centers.

Introduction

Aziridines and azetidines are versatile structural entities in organic synthesis.^[1] Their ring strain is often used as a driving force for S_N2-type ring-opening reactions. This approach has resulted in many practical methods for the synthesis of amine derivatives with various heteroatom-containing groups in their linear chain.^[2] Appropriate design also allows the synthesis of carbonyl compounds.^[3] The combination of electron-rich arynes or heteroarenes with N-activated 2-aziridines induces Friedel-Crafts-type reactions and gives rise to 2,2-dialkyl- or heteroarylalkylamines, respectively.^[4] The S_N2-type ring-opening of aziridines and azetidines followed by various cyclization reactions is a valuable approach for the synthesis of morpholines, oxazepanes and their homologues,^[5] and thiazepin^[6] ring systems. We report herein the efficient SO₂-assisted nucleophilic ring-opening of carbamate-protected aziridines and azetidines. Owing to the fact that these protecting groups are easily cleaved under well-established reaction conditions, this method should be a good addition to the existing ring-opening reactions of aziridines and azetidines.

It is well accepted that an acridone-withdrawing group on a nitrogen atom facilitates the attack of a nucleophile on the neighboring carbon atom of aziridine and azetidine. In fact, the vast majority of aziridine and azetidine ring-opening reactions, including many of those cited above, are described with sulfanyl protecting groups.^[7] However, the removal of the sulfanyl moiety is a rather difficult task.^[8] Other approaches include N-alkylation followed by opening of the quaternary ammonium ion by a halide^[9] or other nucleophile.^[10,11] Carbyl and Evano and co-workers reported the efficient ring-opening

ChemPubSoc Europe DOI: 10.1002/ejoc.201601014

Ritter Reaction

Indium-Triflate-Catalyzed Ritter Reaction of Dioxides

Daniels Posevins,^[a] Krista Suta,^[a] and Māris Turks^[a]

Abstract: The use of liquid sulfur dioxide as a reaction solvent facilitates the Ritter reaction between alcohols and nitriles. In(OH), was found to be a viable catalyst for this transformation. The newly developed catalytic conditions for the Ritter reaction were amides, which catalytic activity liquid sulfur dioxide.

Introduction

The Ritter reaction is a one-pot process for amide formation in which a nitrile reacts with a carbenium ion. The latter can be generated from an alcohol or an alkene in a strongly ionizing medium.^[1] The classical Ritter reaction involves the use of at least a stoichiometric amount of a corrosive Brønsted acid (i.e., H₂SO₄), and as a result, it cannot usually be used with compounds containing acid-labile functional groups.^[2] Nevertheless, because of its atom economy and ease of application, the Ritter reaction is still an important tool in organic synthesis. The Ritter reaction is a one-pot process for amide formation in which a nitrile reacts with a carbenium ion. The latter can be generated from an alcohol or an alkene in a strongly ionizing medium.^[1] The classical Ritter reaction involves the use of at least a stoichiometric amount of a corrosive Brønsted acid (i.e., H₂SO₄), and as a result, it cannot usually be used with compounds containing acid-labile functional groups.^[2] Nevertheless, because of its atom economy and ease of application, the Ritter reaction is still an important tool in organic synthesis.

Prof. Dr. D. Marković, W. A. Tchawou, Dr. S. Lachl, Prof. Dr. P. Vogel

22

SULFUR DIOXIDE: A POWERFUL TOOL FOR THE STEREOSELECTIVE CONSTRUCTION OF C–C BONDS

PIERRE VOGEL, DEAN MARKOVIĆ, AND MĀRIS TURKS

INTRODUCTION

After wood burning, humans discovered that sulfur burning, which produces sulfur dioxide, in jars and other containers would help preserve food and beverages. For a long time, organic chemistry of SO₂ has been limited to the Friedel-Crafts sulfonylation, epoxidation with alkenes, alkyenes, epoxides, and oxetanes.^[1–3] Aresulfonic acids and their salts^[4] are best obtained by reaction of arenes with SO₃(X) (X = SOCl₂ or Al(O)₂Cl₂).^[5] Several methods are available for the preparation of aliphatic sulfonic acids^[6,7] and derivatives including the reaction of organometallic reagents with SO₂. Classically, Grignard^[8,9] and organolithium reagents^[10] have been used, but organoaluminum^[11,12] and organotin^[13] reagents have also been used. More recently, indium,^[14,15] copper,^[16] and transition-metal-carbon compounds^[17,18] can also react with SO₂ to generate sulfonic derivatives. Sulfonates are ambident nucleophiles that react with soft electrophiles (alkyl, benzyl) iodides, Michael acceptors) to produce stable sulfonates (S-alkylation) and with hard electrophiles to give the corresponding sulfonic esters (O-alkylation) or mixed anhydride (O-acylation).^[19–21] Alkyl sulfonates can rearrange into the more stable allylsulfonates, probably via [2,3]-sigmatropic rearrangements as illustrated in Scheme 22.1. Extension of this method to propargyl halides generates allenic sulfonates.

In this chapter, we provide a short review of the use of sulfonates in carbon-carbon, bond-forming reactions. We shall present also less classic reactions of sulfur dioxide and their applications in the development of new reaction cascades that permit diastereoselective C–C bond formation. Applications of the latter to the efficient synthesis of

22.1.1. Reductive Removal of Sulfones

Hydrogenolysis of C–S bonds of sulfones can be realized by H₂ in the presence of a Raney nickel catalyst,^[22–24] by

ChemPubSoc Europe DOI: 10.1002/ejoc.201600141

Aziridine Ring-Opening

Ring-Opening of Carbamate-Protected Aziridines and Azetidines in Liquid Sulfur Dioxide

Jevgeņija Luginja,^[a] Jevgeņija Uzulena,^[a] Daniels Posevins,^[a] and Māris Turks^[a]

Abstract: The reactions of halides or pseudohalides of group I and II metals with carbamate-protected aziridines and azetidines in liquid sulfur dioxide as solvent resulted in the efficient ring-opening of these heterocycles. Sulfur dioxide, as a highly polar solvent, solubilizes the inorganic salts and acts as a Lewis acid to accelerate the ring-opening. For this reason, carbamate-protected small heterocycles can be used instead of the corresponding sulfonamides, the activities of which are well-established in ring-opening reactions. This also performed well in the SO₂-assisted ring-opening of aziridines. This procedure occurred without racemization of the stereogenic centers.

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Stereoselective Synthesis of Drugs And Natural Products

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