Methyl 4-Pentafluorosulfanylphenyl Sulfoximines

Christine M. M. Hendriks
Jens Reball
Carsten Bolm*

Institute of Organic Chemistry, RWTH Aachen University, Landoltweg 1, 52074 Aachen, Germany
carsten.bolm@oc.rwth-aachen.de

Abstract

A low-cost and high-yielding synthetic route towards methyl 4-pentafluorosulfanylphenyl sulfoximines from the corresponding sulfide has been developed. The intermediate N-cyano sulfoxime was converted into the corresponding N(1H)-tetrazole, and the NH-sulfoxime was modified by N-arylation and N-alkylation reactions.

Key words

building blocks, pentafluorosulfanyl group, sulfoximine, organofluorine compounds, sulfilimine

Fluorine-containing compounds exhibit unique physicochemical properties and, consequently, they are of interest in medicinal chemistry, crop protection, and material sciences.† In this context, the pentafluorosulfanyl group (SF₅), also known as ‘super-trifluoromethyl’ group, plays a very special role.‡ Noteworthy are, for example, the high thermal stability of aryl sulfurpentfluorides and the chemical inertness of the SF₅ group towards hydrolysis.§ Compared with a trifluoromethyl substituent, the SF₅ group has a higher electronegativity¶ and polarity, and the respective molecules show improved lipophilicity.‖ As a result, the SF₅ group has become an attractive structural motif in the design of biologically active compounds,‡ ³⁶ functional materials,¶ and, as recently reported, in Brønsted acid catalysts.§

Due to the fact that only a few efficient synthetic methods for the introduction of the SF₅ group exist,³ ³⁶ commercially available SF₅-containing building blocks are rare and most of them are expensive. Therefore, the development of new scaffolds with SF₅ groups appears to be desirable.

Sulfoximines, the mono-aza analogues of sulfones, are widely used in asymmetric synthesis and catalysis.¹⁰ Especially in the last years, such compounds have also attracted attention as drugs¹¹ and crop protection agents.¹² Advantageously, in contrast to sulfones, they are modifiable at the sulfoximine nitrogen, which can lead to beneficial effects on the solubility of the respective molecules.¹³ Fluorine-containing sulfoximines¹¹,¹²,¹⁴–¹⁶ are of particular interest because they combine the advantages of the sulfoximidoyl moiety with the favorable electronic and steric properties induced by, for example, a fluoro or a trifluoromethyl substituent. However, to our knowledge, sulfoximines bearing SF₅ groups are unprecedented. Here, we fill this synthetic gap and report on preparative routes towards a range of key compounds with sulfoximidoyl cores and SF₅ substituents.

For the preparation of the first target molecule (NH-sulfoximine 4), methyl 4-pentafluorosulfanylphenyl sulfide (1) was regarded as a promising starting material.¹⁷ Fulfilling our expectations, the imination of 1 with cyanamide and N-bromosuccinimide (NBS)¹⁸ proceeded smoothly, affording the corresponding N-cyano sulfilimine 2 in 96% yield (Scheme 1). Subsequent oxidation with m-CPBA¹⁸ led to N-cyano sulfoxime 3 in 81% yield. Finally, the CN-group was cleaved upon treatment with 50% aq. H₂SO₄ at 110 °C,¹⁹ providing the desired NH-sulfoximine 4 in 71% yield.²⁰ Both enantiomers of the racemic mixture could be separated on analytical CSP HPLC, which allowed 4 to be obtained in non-racemic form by preparative HPLC separation.²¹

Scheme 1 Synthesis of methyl 4-pentafluorosulfanylphenyl sulfoximine 4

Considering that N-arylated sulfoximines can be highly selective ligands in asymmetric metal catalysis,¹⁰,²² we first investigated the application of a representative N-phenylation protocol allowing the conversion of 4-pentafluorosulfanylphenyl sulfoxime (4) into N-arylated sulfoximine 5 under copper catalysis.²³ To our delight, this approach was
highly efficient, providing N-phenyl sulfoximine 5 in 93% yield starting from 4 and iodo benzene as aryl source (Scheme 2).

We then focused on the N-methylation of 4 to give 6. This transformation was regarded as particularly important because it was recently demonstrated that several N-methyl sulfoximines showed a significantly higher solubility compared with their isomeric counterparts in the sulfone series, leading to beneficial effects in their respective bioactivity studies. Here, the N-methylation of 4 was successfully performed under Eschweiler–Clark conditions, affording N-methylated sulfoximine 6 in 78% yield (Scheme 2).

Considering that tetrazoles are carboxylic acid bioisosteres that often exhibit high bioactivities, the conver- sion of N-cyano sulfoximine 3 into tetrazole 7 was studied.

By using a combination of NaN₃ and ZnBr₂ in methanol– water, formation of the heterocycle proceeded smoothly, leading to N-(1H)-tetrazole methyl 4-pentafluorosulfanylphenyl sulfoximine (7) in 62% yield (Scheme 2).

The three representative synthetic transformations depicted in Scheme 2 allow us to draw two significant conclusions: first, compounds such as 4 are readily available; and second, standard protocols can be used for modifications of sulfoximines with 4-pentafluorosulfanyl substituents providing interesting new building blocks for future synthetic and biological applications.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1016/j.sol.2019.1378936.

References and Notes


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(20) Synthesis of NH-Sulfoximine 4 from Sulfide 1; General Procedure: Step 1: To a solution of 1 (1.0 mmol) in MeOH (6 mL), was added NH3CN (76 mg, 1.8 mmol), t-BuOK (191 mg, 1.7 mmol) and NBS (356 mg, 2.0 mmol). The reaction was stirred at room temperature until the starting material was consumed (reaction monitored by TLC). After removing the solvent under reduced pressure, water (10 mL) was added and the mixture was extracted with CH2Cl2 (3 × 20 mL). The combined organic layers were dried over anhydrous magnesium sulfate and the solvents were removed under reduced pressure. Purification by flash column chromatography provided N-cyanosulfilmine 2. Step 2: To a solution of 2 (0.3 mmol) in EtOH (2.7 mL) was added m-CPBA (ca. 70%, 101 mg, 0.45 mmol). The reaction mixture was stirred at room temperature until the starting material was consumed (reaction monitored by TLC). After removing the solvent under reduced pressure, H2O (5 mL) was added and the mixture was extracted with CH2Cl2 (3 × 10 mL). The combined organic layers were dried over anhydrous magnesium sulfate and the solvents were removed under reduced pressure. Purification by flash column chromatography provided N-cyanosulfoximine 3. Step 3: A solution of 3 (0.23 mmol) in 50% aq H2SO4 (2.3 mL) was stirred at 110 °C for 2 h. After cooling to room temperature and adjusting the pH to 9 by addition of eq. sat NaHCO3 and eq. sat NaOH solution, the mixture was extracted with CH2Cl2 (3 × 20 mL) and the combined organic layers were dried over anhydrous magnesium sulfate and the solvents were removed under reduced pressure. Purification by flash column chromatography provided NH-sulfoximine 4.

(21) For HPLC analytical data, see the Supporting Information.

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