BUDAPEST UNIVERSITY OF TECHNOLOGY AND ECOOMICS
FACULTY OF CHEMICAL TECHNOLOGY AND BIOTECHNOLOGY
GEORGE A. OLAH DOCTORAL SCHOOL

Synthesis and rearrangements of 1,2,3-benzothiadiazine 1,1-dioxide derivatives

Thesis booklet

Author: Imre Gyűjtő

Supervisor: Balázs Volk, PhD, DSc

Advisors: Márta Porcs-Makkay, PhD

Gyula Simig, PhD, DSc

László Nyulászi, PhD, DSc

Egis Pharmaceuticals Plc., Directorate of Drug Substance Development

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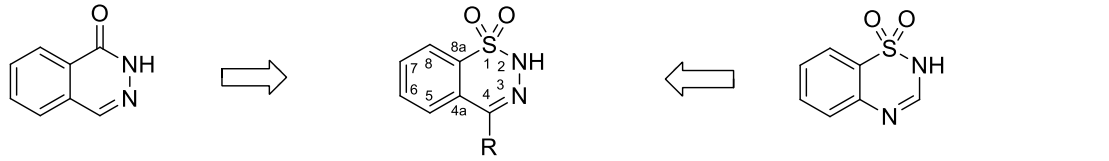
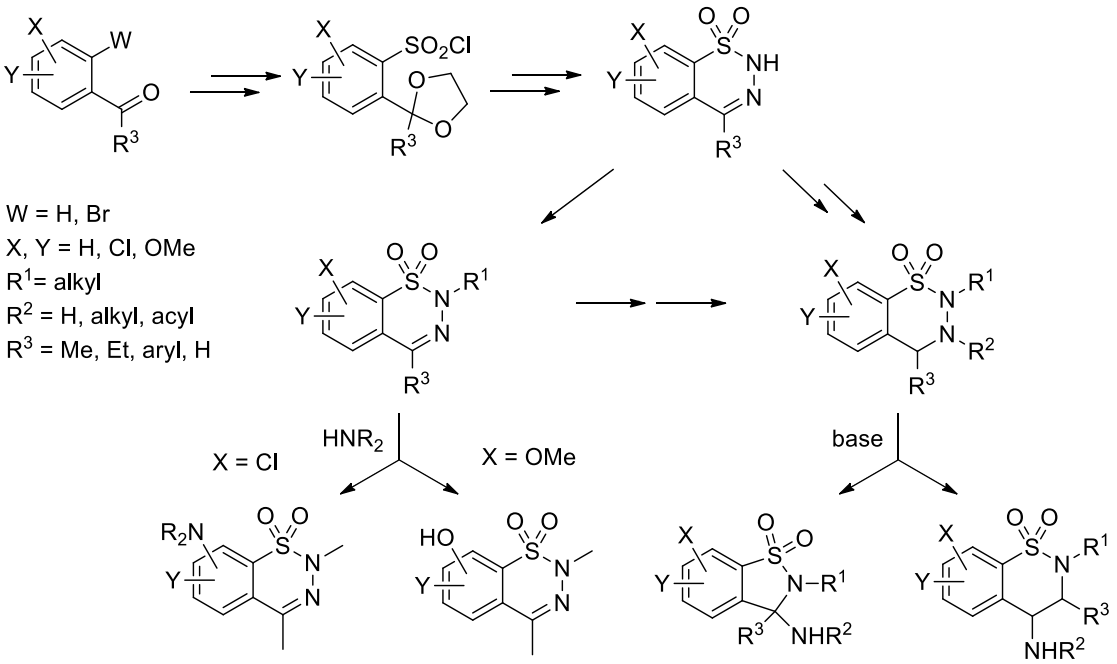
1. Introduction

Research was initiated for the development of 2*H*-1,2,3-benzothiadiazine 1,1-dioxides (BTDs) potentially exhibiting CNS activity (Scheme 1) at Egis Pharmaceuticals around 20 years ago. This heterocycle is structurally related to phthalazinone and 1,2,4-benzothiadiazine 1,1-dioxide drug scaffolds (present in e.g. olaparib, talazoparib, and chlorothiazide, hydrochlorothiazide). In addition, BTD can serve as a core structural unit to which pharmacophores can be attached.



Scheme 1. The pharmacological motivation of the development of BTDs.



Scheme 2. The objectives of the dissertation.

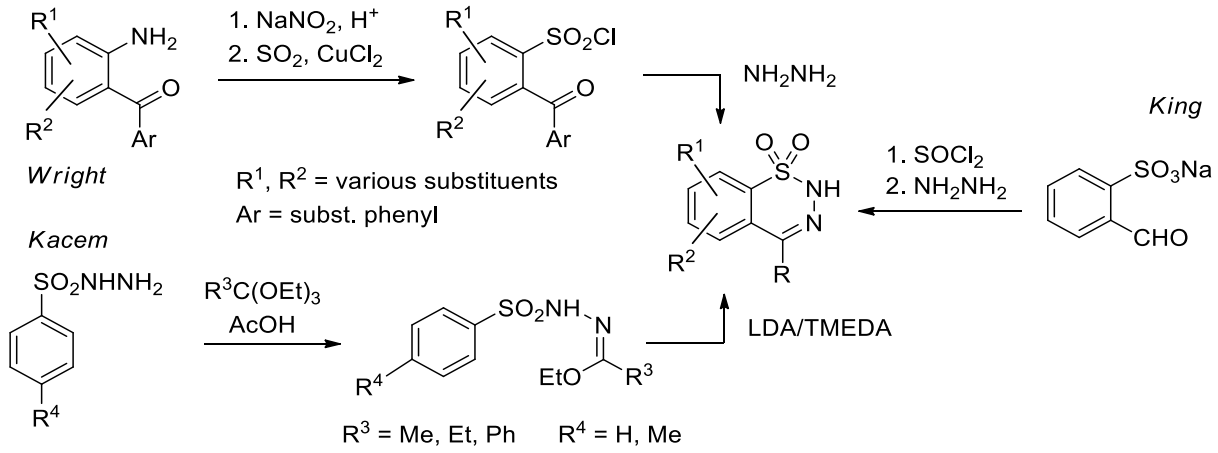
Although interesting chemical aspects were discovered in the course of the synthesis of these compounds, there was no opportunity for their detailed investigation. Therefore, the aim of my PhD research was to widen the scope of the prepared BTDs, to present improved synthetic routes,

and to study the surprising discoveries emerging during the research. The BTD derivatives were constructed from aceto- and benzophenone ketals and benzaldehyde acetals (Scheme 2), and their *N*-alkylation, reduction and reaction with amines (nucleophilic substitution and *O*-demethylation) were elaborated. The other area to be explored was the rearrangement reactions of BTDs to 1,2-benzisotihazole 1,1-dioxides and 1,2-benzothiazine 1,1-dioxides.

2. Literature

Construction of the BTD core and reactions thereof

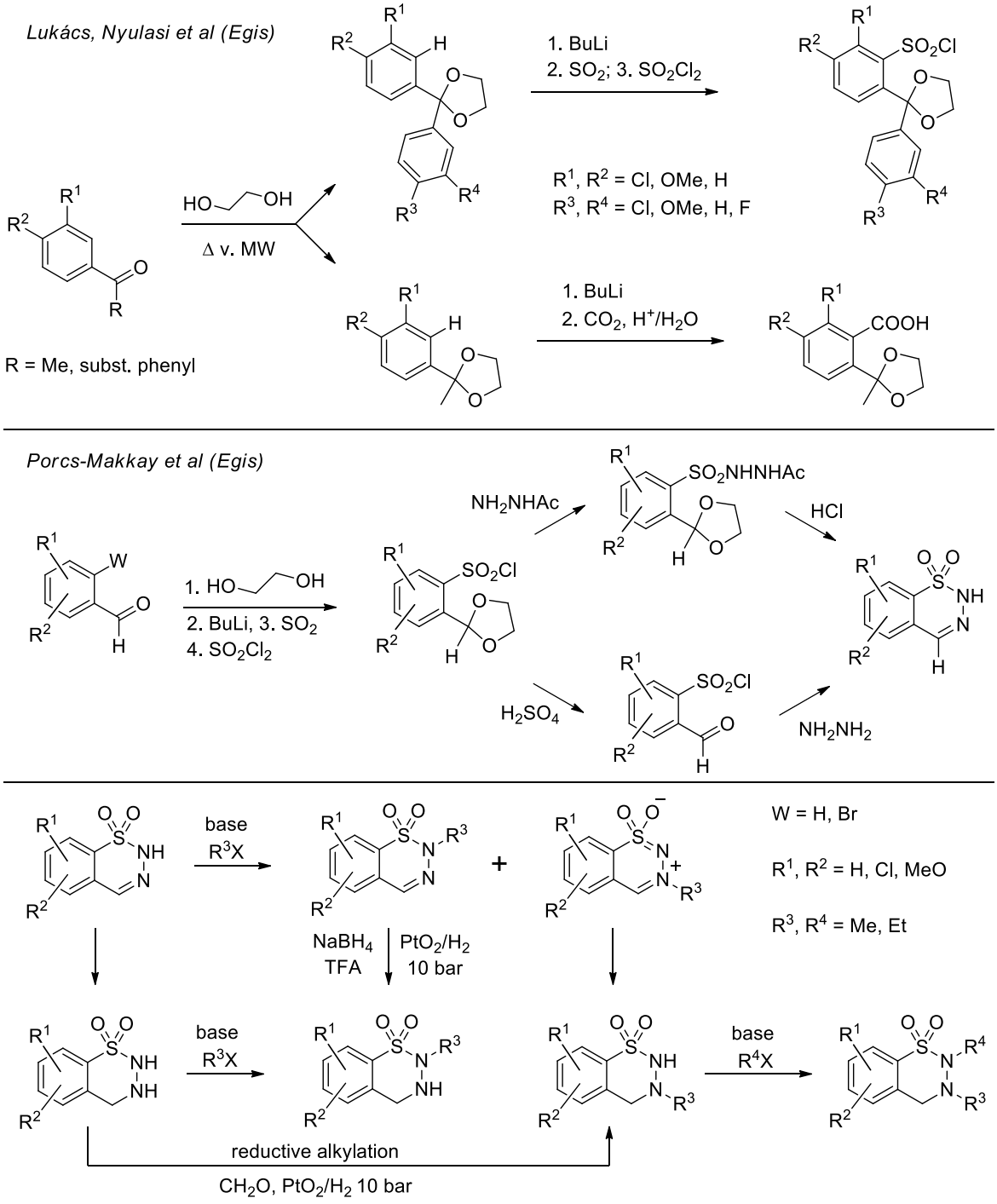
The literature on the synthesis of the BTD compound family is rather scarce, only a few approaches were published (Scheme 3). Wright et al prepared BTDs via diazotation of *o*-aminobenzophenones and subsequent reaction with SO_2 and $CuCl_2$, followed by ring closure with hydrazine.[1] According to an alternative synthesis by King, sodium 2-formylbenzenesulfonate was employed as the starting material.[2] Kacem's synthetic strategy was based on the *ortho* lithiation of N^1-arylsulfonylhydrazonates with LDA in the presence of TMEDA.[3]



Scheme 3. Literature syntheses of BTDs

[1] Wright, J. B.; Kalamazoo, M. *US 3407197 US Pat. Appl.; Chem. Abstr.* **1969**, *70*, 57914.
[2] King, J. F.; Hawson, A.; Deaken, D. M.; Komery, J. *Chem. Commun.* **1969**, *1*, 33–34.
[3] Kacem, Y.; Hassine, B. B. *Tetrahedron Lett.* **2013**, *54*, 4023–4025.

A lithiation-based methodology was elaborated starting from commercially available aceto- and benzophenones and benzaldehydes by the researchers of Egis in order to afford variously substituted BTDs (Scheme 4).



Scheme 4. Process for the *ortho* lithiation of ketals (above), for the synthesis of 4-H BTDs (middle), and the alkylation and reduction thereof (below) elaborated at Egis Pharmaceuticals.

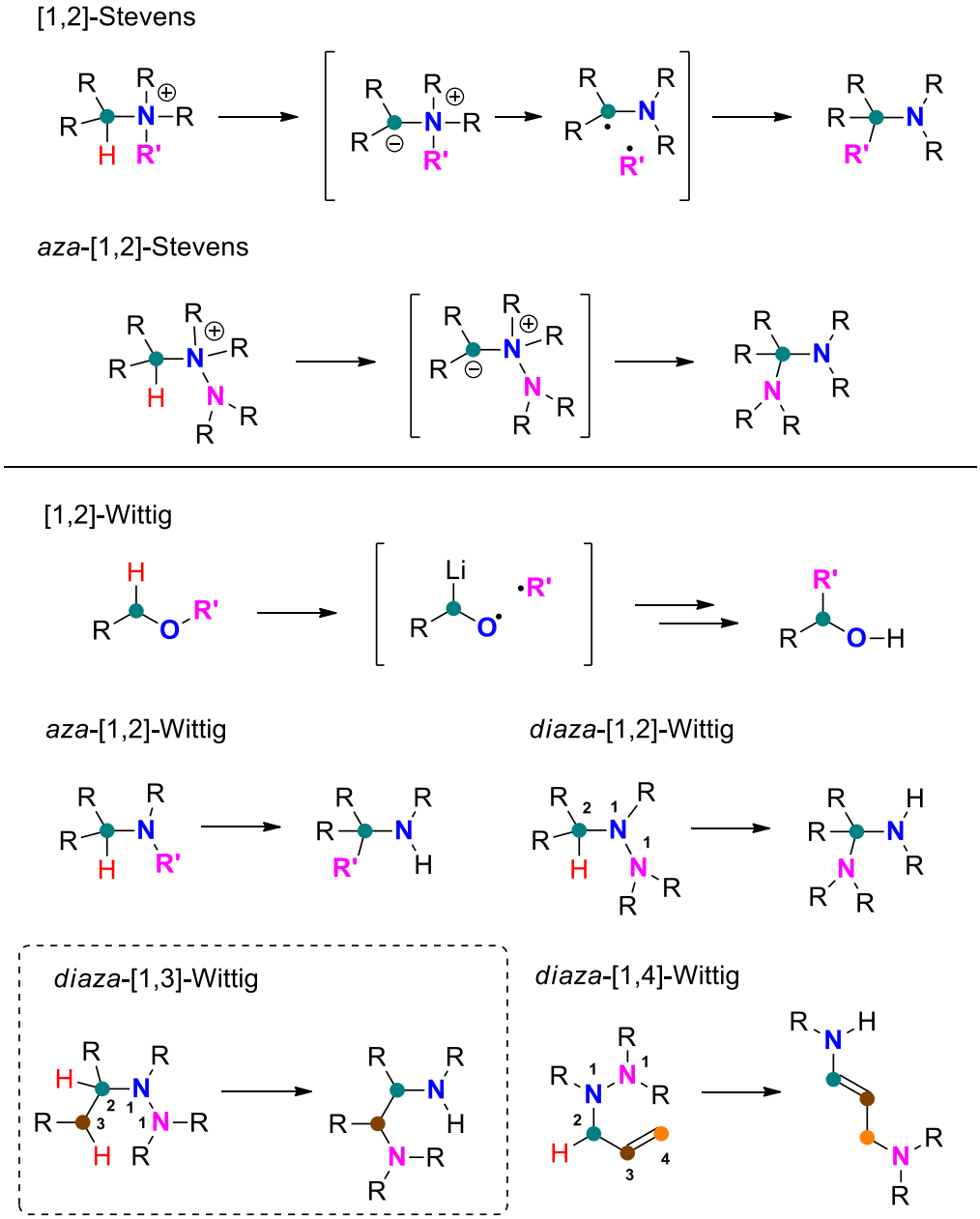
The carbonyl group was protected with ethylene glycol (typically under microwave irradiation) to give the corresponding 1,3-dioxolanes (Scheme 4, above).[4] The synthesis of sulfonyl chlorides was elaborated via lithiation of ketals with BuLi followed by consecutive treatment of the obtained aryllithium species with sulfur dioxide and sulfuryl chloride. This strategy was demonstrated on variously substituted benzophenone ketals.[5] As far as acetophenone ketals are concerned, mainly carbon dioxide was employed as the electrophile to map the regioselectivity,[6] and only a few examples were published using sulfur dioxide. In case of 4-unsubstituted (4-H) BTDs (Scheme 4, middle), for the ring closure of the 2-chlorosulfonyl acetals obtained in similar manner, two methods were elaborated: using either hydrazine or acethydrazide, and the protective group removal was conducted under acidic conditions.[7] Alkylation of 4-H BTDs led to the formation of both *N*(2)-alkyl and mesoionic *N*(3)-alkylated products (Scheme 4, below).[8] The C=N double bond was reduced with $NaBH_4$/TFA or PtO_2/H_2 systems. Reductive alkylation was performed with paraformaldehyde to introduce a methyl group into position 3.

Stevens- and Wittig rearrangements

[1,2]-Stevens rearrangement of quaternary ammonium salts involves a base-induced deprotonation at the α-carbon atom followed by a [1,2]-migration most probably via a biradical mechanism (Scheme 5).[9] Hydrazinium compounds undergo a base-promoted *aza*-[1,2]-Stevens rearrangement in a similar fashion.[10] In case of the [1,2]-Wittig rearrangement, after α-deprotonation the C–O bond is cleaved and a [1,2]-migration occurs.[11] The main structural difference between the reactants of the Stevens and the *aza*-analogues of Wittig rearrangement is that in the latter there is no quaternary nitrogen. During the *aza*-[1,2]-Wittig rearrangement, the C–N bond breaks. Continuing the series of rearrangements, one could call similar transformations involving the cleavage of N–N bonds *diaza*-[1,2]-Wittig rearrangements (e.g. the ring expansion

[4] Lukács, G.; Porcs-Makkay, M.; Komáromi, A.; Simig, G. *Arkivoc* **2008**, *iii*, 17–24.
[5] Lukács, G.; Porcs-Makkay, M.; Simig, G. *Eur J. Org. Chem.* **2004**, *20*, 4130–4140.
[6] Nyulasi, B.; Németh, A.; Porcs-Makkay, M.; Kupai, J.; Lukács, G.; Simig, G.; Volk, B. *Tetrahedron* **2017**, *73*, 298–306. Lukács, G.; Porcs-Makkay, M.; Simig, G. *Tetrahedron Lett.* **2003**, *44*, 3211–3214.
[7] Porcs-Makkay, M.; Lukács, G.; Pandur, A.; Simig, G.; Volk, B. *Tetrahedron* **2014**, *70*, 286–293.
[8] Porcs-Makkay, M.; Kapiller-Dezsőfi, R.; Párkányi, L.; Pandur, A.; Simig, G.; Volk, B. *Tetrahedron* **2014**, *70*, 2169–2174. Porcs-Makkay, M.; Pandur, A.; Simig, G.; Volk, B. *Tetrahedron* **2015**, *71*, 44–50.
[9] Bach, R.; Harthong, S.; Lacour, J. *Nitrogen- and Sulfur-Based Stevens and Related Rearrangements*; Elsevier Ltd., 2014.
[10] Nakamura, A.; Kamiya, S. *Chem. Pharm. Bull.* **1974**, *22*, 2142–2146.
[11] Wolfe, J. P. *The Wittig Rearrangement*; Elsevier Ltd., 2014; Vol. 3.

of *N*-fluorenylurazoles with *t*-BuOK). [12] The *diaza*-[1,4]-Wittig rearrangement is a known transformation,[13] while the *diaza*-[1,3]-Wittig rearrangement is a missing link.



Scheme 5. Stevens- and Wittig rearrangements, and their *aza*-analogues.

[12] Gong, Y.; Bausch, M. J.; Wang, L. *Heterocycles* **2001**, *55*, 163–170.
[13] Tayama, E.; Kobayashi, Y.; Toma, Y. *Chem. Commun.* **2016**, *52*, 10570–10573.

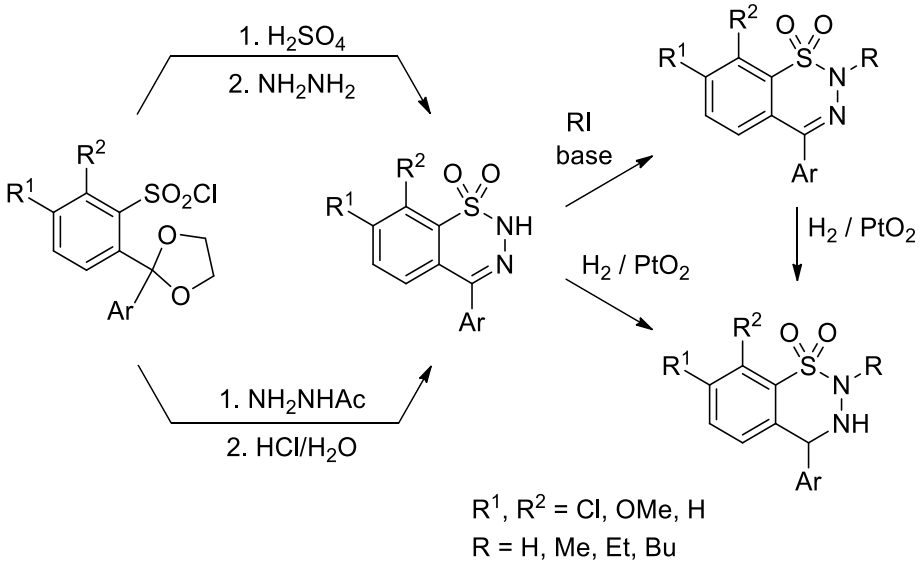
3. Experimental and computational methods

The experimental work was carried out in a preparative organic chemistry laboratory using standard equipment, by performing classical and state-of-art synthetic techniques. Lithiation was conducted under argon atmosphere, sulfur dioxide was delivered from a cylinder. A Milestone MicroSYNTH® multimode microwave reactor was used for the preparation of ketals, while catalytic hydrogenation was conducted in autoclaves. Reactions were followed by TLC, HPLC-MS, GC-MS or NMR. The prepared compounds were purified by vacuum distillation, flash chromatography or recrystallization. Structures were identified by NMR (^{1}H, ^{13}C, DEPTQ, HSQC, HMBC, 1D selNOE; Bruker TopSpin 3.5 software), IR, HRMS, EA and sc-XRD measurements.

DFT calculations were carried out with the Gaussian 09 software package. B3LYP and M06-2X functional was used in conjunction with the 6-31G or 6-31+G* basis set for conformational analysis on all reactants and intermediates to identify the most plausible conformers. For frequency calculations, an ultrafine grid was used, and free energies are reported in kcal/mol at 1 atm and 25 °C. Free energies for gas-phase acidity were calculated with fine grid and $G(H^{+}(gas)) = -6.28$ kcal/mol was used. Normal mode analysis has been performed, as well as Intrinsic Reaction Coordinate (IRC) calculations to verify the transition state geometries. The possible pathways under study were modelled using the SMD or PCM solvent models. Diffuse functions were employed in case of anions, the stability of the wavefunctions was checked and the energies of anions and the corresponding radicals were compared to evade unnoticed electron loss. The Avogadro software was used for the visualization of Kohn–Sham molecular orbitals and CYLview for geometries.

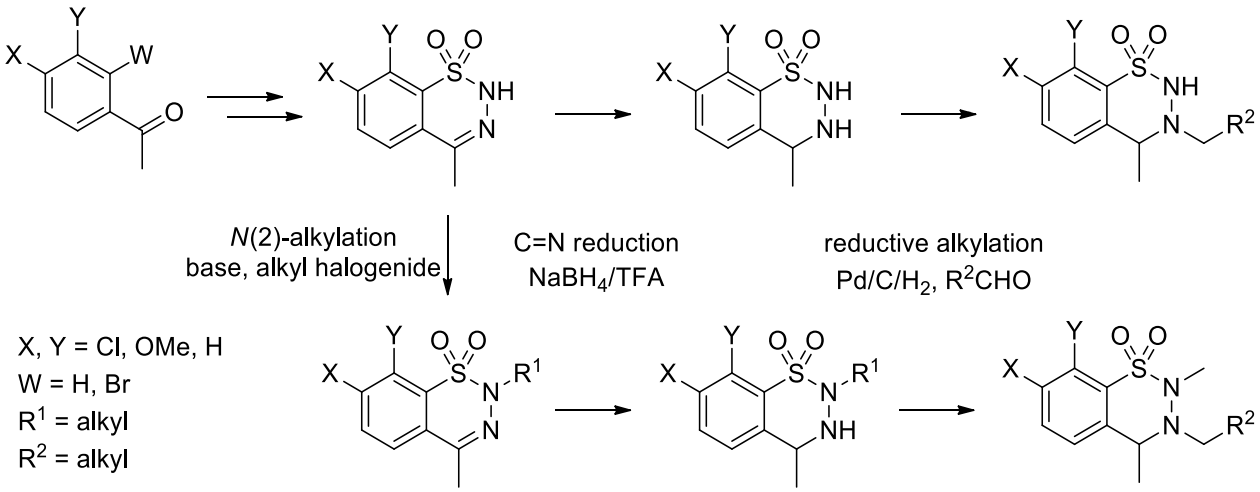
4. Results

4-Aryl-BTDs were obtained via the ring closure of the corresponding chlorosulfonyl ketals using hydrazine or acethydrazide (Scheme 6). 3,4-Dihydro and/or 2-alkyl derivatives seemed promising based on pharmacological tests. Therefore, the C=N double bond was hydrogenated in the presence of PtO_2. 2-Alkylation reactions were conducted using NaH or *t*-BuOK bases and alkyl iodides to introduce 2-methyl, -ethyl and -butyl groups. It occurred with good regioselectivity compared to the 4-H BTDs, when the *N*(2)- and *N*(3)-alkylated products were formed in roughly same amount. *N*(2)-Alkylation with 1-bromo-4-chlorobutane allowed the introduction of a pharmacophore by nucleophilic replacement of the terminal leaving group.



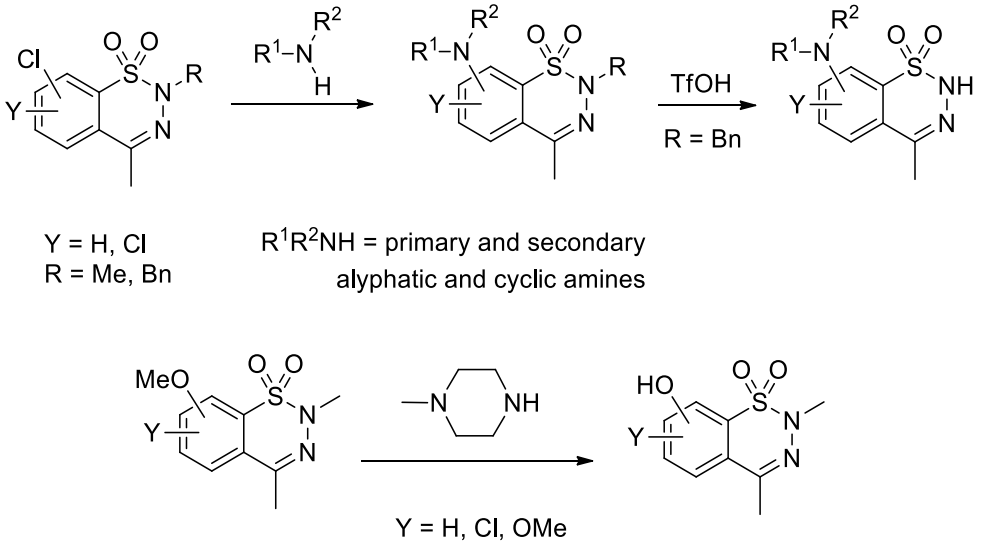
Scheme 6. Synthesis, reduction and alkylation of 4-aryl-BTDs

A process was elaborated for the preparation of 4-methyl-BTDs starting form acetophenones (Scheme 7). The carbonyl group was protected as a dioxolane with ethylene glycol under MW conditions or with triethyl orthoformate. Sulfonyl chlorides were prepared by trapping the corresponding aryllithiums with sulfur dioxide, followed by treatment of the isolated aryl sulfinate with sulfuryl chloride. In case of the unsubstituted and the *para*-methoxy substituted acetophenone, the *ortho*-bromo derivatives were used as the starting materials, and a bromine-lithium exchange took place. The protecting group was removed under acidic conditions and the ring closure was conducted with hydrazine or acethydrazide. *N*(2)-Alkylation was conducted with methyl-, ethyl- and benzyl halogenides. The reduction of *N*(2)-unsubstituted or -alkylated compounds were performed with $NaBH_4$/TFA instead of catalytic hydrogenation in the presence of PtO_2. Alkyl groups were introduced to position 3 via reductive alkylation with aldehydes in the presence of palladium on charcoal under hydrogen atmosphere. Based on the elaborated process, 2,4-dimethyl-3,4-dihydro compound could be transformed to the 3,4-saturated 2,3,4-trimethyl derivative. In the NMR spectra of the 3,4-dihydro congeners, a line broadening (or even the disappearance of ^{13}C peaks) were observed and explained by conformational behaviours: the degree of ring inversion is influenced by the substituents of the nitrogen atoms (at positions 2 and 3) and by those of the aromatic ring at position 8.



Scheme 7. Synthesis of 4-methyl-BTDs and their alkylation and reduction reactions

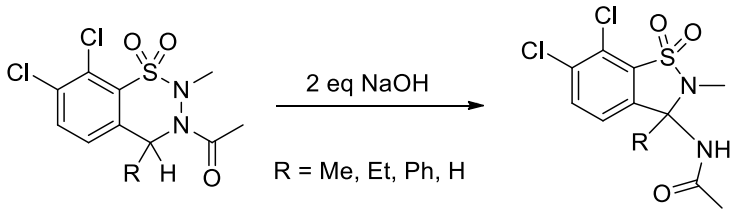
Furthermore, 7- and/or 8-chloro substituted 2,4-dimethyl-BTDs were reacted with amines to give the corresponding 7- or 8-amino compounds (Scheme 8). Reaction of 7,8-dichloro-2,4-dimethyl-BTD afforded a mixture of regioisomers in most cases: secondary amines could be mainly introduced to the sterically less crowded position 7, whereas primary amines were more likely to attack at the electronically more favoured position 8. Structure determination of the regioisomers was carried out using 1D selNOE and detailed 2D NMR techniques. In addition, the conformational behaviour was clarified: the ring inversion of cyclic amines is fast at position a 7, whereas at position 8 it cannot take place due to steric hindrance.



Scheme 8. Reaction of chloro- and methoxy-BTDs with amines.

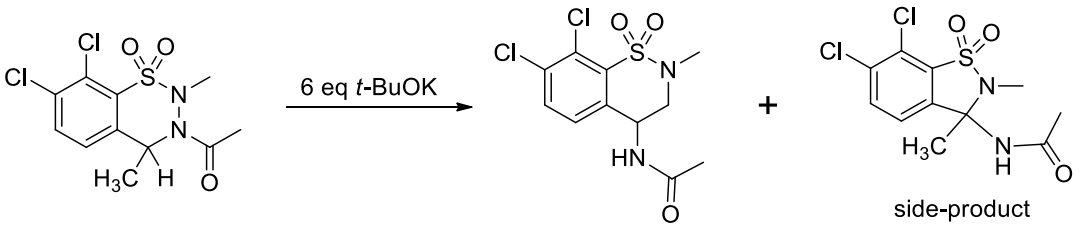
We also aimed at the synthesis of 2-unsubstituted BTDs bearing an amino group at the aromatic ring. Benzyl group was employed as a protecting group to withstand the harsh conditions of the chlorine–amine exchange reaction. The debenzylation was performed with trifluoromethanesulfonic acid at 100 °C (Scheme 8). In the reaction of 8-chloro-2,4-dimethyl-7-methoxy-BTD with amines, *O*-demethylation occurred leading to the corresponding phenol, instead of substitution of the chlorine atom (Scheme 8). The *O*-demethylation was also demonstrated on other methoxy-BTDs using *N*-methylpiperazine.

Attempted reduction of the acetyl moiety of 3-acetyl-7,8-dichloro-2,4-dimethyl-3,4-dihydro-BTD with $LiAlH_4$ led surprisingly to the corresponding 2,3-dihydro-1,2-benzisothiazole 1,1-dioxide, a ring-contracted product. Thus, $LiAlH_4$ did not act as a reducing agent but as a base in the reaction. This base-mediated rearrangement was then extended to other substituents (H, Et, Ph) in position 4 using 2 eq solid NaOH in THF with high yields (Scheme 9).



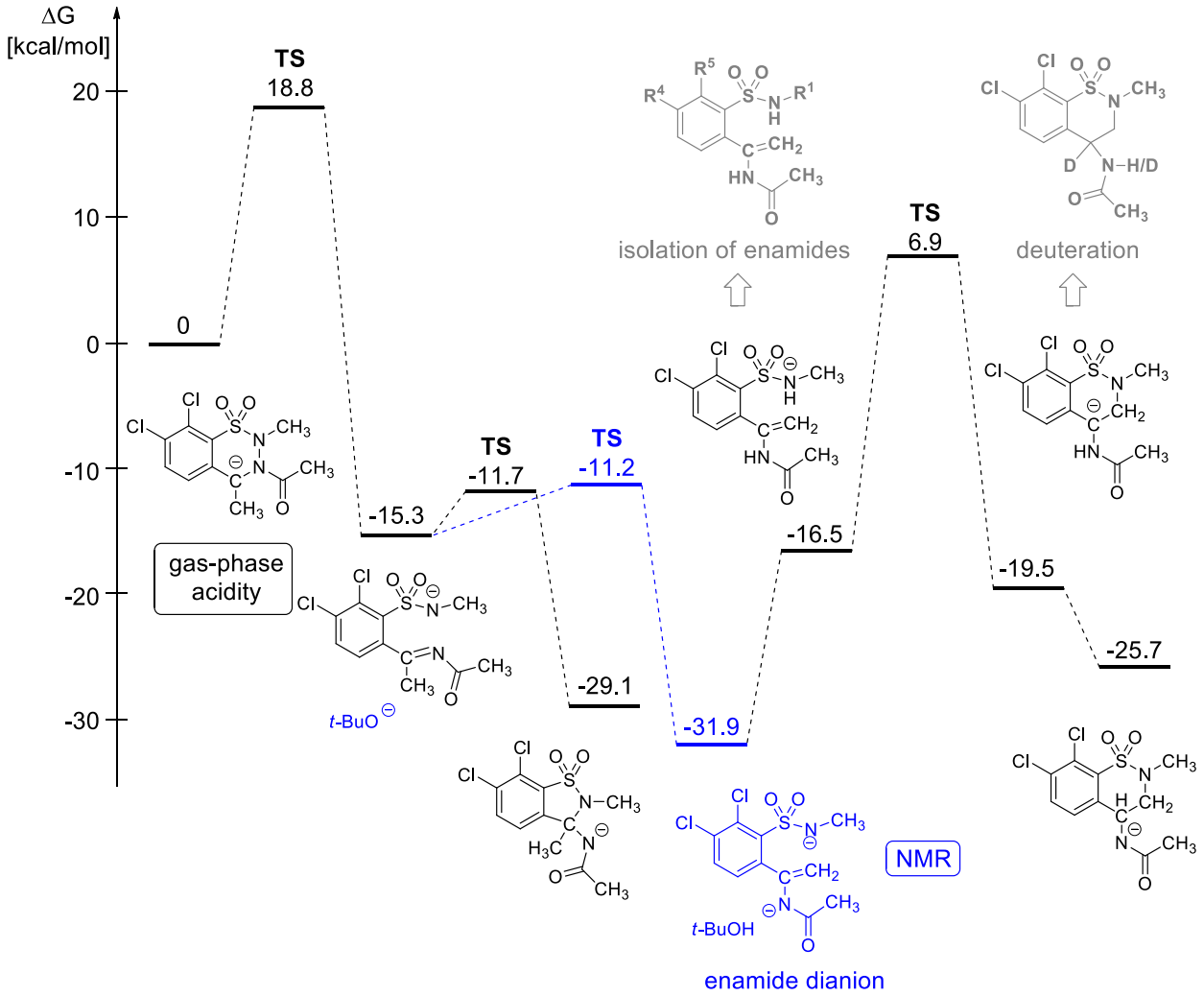
Scheme 9. Ring contraction of 3-acetyl-7,8-dichloro-2-methyl-3,4-dihydro-BTDs with NaOH.

Treatment of 3-acetyl-7,8-dichloro-2,4-dimethyl-3,4-dihydro-BTD with 6 eq *t*-BuOK in THF gave rise to the formation of the corresponding 1,2-benzothiazine 1,1-dioxide as the major product besides the 1,2-benzisothiazole 1,1-dioxide (Scheme 10). The effect of reaction conditions (including e.g. solvent, base and the amount thereof) were investigated on the product selectivity of the two ring transformations. We found that strongly basic conditions were necessary for the formation of benzothiazine, otherwise benzisothiazole would be the sole product.



Scheme 10. Rearrangement of 3-acetyl-7,8-dichloro-2,4-dimethyl-3,4-dihydro-BTD to the corresponding benzothiazine 1,1-dioxide.

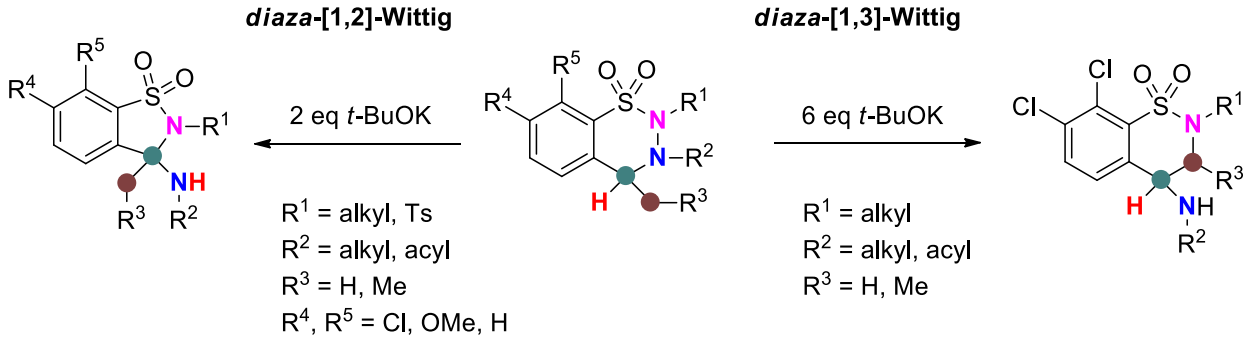
The mechanism of a monoanionic pathway was calculated which fully justified the formation of benzisothiazole on thermodynamic as well as on kinetic grounds (Scheme 11). The key intermediate of the proposed route toward benzothiazine was an enamide dianion, which was supported by NMR studies. The presence of a benzothiazine carbanion intermediate was proved by trapping with D_2O, as well. The reversibility of the rearrangements was investigated, and revealed that the treatment of benzisothiazole with 6 eq *t*-BuOK induced a ring opening resulting in benzothiazine.



Scheme 11. DFT studies on the reaction mechanism at M06-2X/6-31+G* (SMD: THF) level of theory, and experimental proofs of the proposed intermediates.

After that, we intended to widen the substrate scope (Scheme 12). The substituent effect was evaluated experimentally on the outcome of the rearrangements. Using 2 eq *t*-BuOK in THF, the

diaza-[1,2]-Wittig rearrangement was extended to substrates bearing alkyl or tosyl groups at position 2, alkyl or acyl groups at position 3, and various substituents at the aromatic ring (Cl, OMe, H at position 7 and 8). Modifications in the aromatic substitution pattern (in respect to the 7,8-dichloro derivative) resulted in enamides as the main products in the rearrangement reaction (Scheme 11). Cyclization could be fostered by quenching with 1% HCl or by heating (Scheme 12). A targeted preparative process was elaborated for *diaza*-[1,3]-Wittig rearrangement of 3-acyl-2,4-dialkyl-7,8-dichloro-3,4-dihydro-BTDs.



Scheme 12. *Diaza*-[1,2]- és *diaza*-[1,3]-Wittig rearrangement reactions of BTDs.

5. Theses

1. Two methods were elaborated for the synthesis of 4-aryl-2*H*-1,2,3-benzothiadiazine 1,1-dioxides starting from the ethylene ketals of the corresponding 2-aroylbenzenesulfonyl chlorides, which were cyclized with hydrazines. The products thus obtained were transformed into their 3,4-dihydro congeners via hydrogenation, and were alkylated regioselectively in the presence of bases to give 2-alkyl derivatives.[P2]

2. Two processes were developed for the preparation of 4-methyl-2*H*-1,2,3-benzothiadiazine 1,1-dioxides starting from acetophenones. *Ortho* lithation of the corresponding ethylene ketals gave access to 2-acetylbenzenesulfonyl chloride key intermediates. The ring closure was performed using hydrazine or acethydrazide. Methods were elaborated for the reduction of the C=N double bond, and *N*(2)- or *N*(3)-alkylation. A line broadening was observed in the ^{1}H and ^{13}C spectra of corresponding 3,4-dihydro congeners, and it was discussed in detail. [P3]

3. A process was elaborated for the synthesis of 7- and 8-amino-2,4-dimethyl-1,2,3-benzothiadiazine 1,1-dioxides starting from the corresponding 7- and 8-chloro compounds. In case

of 7,8-dichloro derivatives, reactions with primary amines gave 8-amino, whereas secondary amines afforded the 7-amino derivatives as the main products. 2-Unsubstituted 7- or 8-amino-2*H*-1,2,3-benzothiadiazine 1,1-dioxides were prepared from the corresponding 2-benzyl derivative via amination and subsequent debenzylation. Structure determination of the regioisomers was carried out using comprehensive NMR techniques, and the conformational behaviour of the amino substituents was studied, as well.

4. A synthetic method was elaborated for the *O*-demethylation of 7-methoxy, 8-methoxy and 7,8-dimethoxy 2,4-dimethyl-2*H*-1,2,3-benzothiadiazine 1,1-dioxides in refluxing *N*-methylpiperazine. [P5]

5. The base-mediated rearrangement of 3-acetyl-7,8-dichloro-2,4-dimethyl-3,4-dihydro-2*H*-1,2,3-benzothiadiazine 1,1-dioxide to the corresponding 1,2-benzisothiazole 1,1-dioxide was observed and explored. The ring contraction was extended to variously substituted 3,4-dihydro-2*H*-1,2,3-benzothiadiazine 1,1-dioxides using 2 eq NaOH or *t*-BuOK. [P1, P6]

6. We found that the treatment of 3-acetyl-7,8-dichloro-2,4-dimethyl-3,4-dihydro-2*H*-1,2,3-benzothiadiazine 1,1-dioxide with 6 eq *t*-BuOK gave rise to the formation of the corresponding 1,2-benzothiazine 1,1-dioxide as the major product. The effects of reaction conditions and substituents on the outcome of the reaction were investigated in detail. A plausible mechanism was proposed based on DFT and NMR studies. Furthermore, a targeted preparative method was elaborated for the rearrangement of 3-acyl-2,4-dialkyl-7,8-dichloro-3,4-dihydro-2*H*-1,2,3-benzothiadiazine 1,1-dioxides to 1,2-benzothiazine 1,1-dioxides. [P6]

6. Application of the scientific results

During my PhD research, I elaborated processes for the preparation of variously substituted benzothiadiazine 1,1-dioxides and their 3,4-dihydro congeners. The synthesized compounds are drug-like themselves, moreover they can be further functionalized at the aromatic ring and at positions *N*(2) and *N*(3) to transform them to other drug candidates based on our synthetic methods. Our studies significantly contributed to the exploration of the chemistry of benzothiadiazine 1,1-dioxides and to that of *diaza*-Wittig rearrangements.

7. Publications

Scientific publications related to the PhD thesis

[P1] Porcs-Makkay, M.; Gyűjtő, I.; Simig, G.; Volk, B.: **Synthesis and base-mediated rearrangement of 3-acetyl-2-methyl-3,4-dihydro-2*H*-1,2,3-benzothiadiazine 1,1-dioxides.** *Tetrahedron* **2016**, *72*, 8463–8469. DOI: 10.1016/j.tet.2016.11.021. IF[2016]: 2.651. (contribution: 100%)

[P2] Porcs-Makkay, M.; Gyűjtő, I.; Lukács, G.; Komáromi, A.; Tóth, G.; Garádi, Z.; Simig, G.; Volk, B. **Synthesis, Alkylation and Reduction of 4-Aryl-2*H*-1,2,3-benzothiadiazine 1,1-dioxides.** *Chemistry Select* **2019**, *4*, 8295–8300. DOI: 10.1002/slct.201901212. IF[2019]: 1.811. (contribution: 95%)

[P3] Gyűjtő, I.; Porcs-Makkay, M.; Lukács, G.; Pusztai, G.; Garádi, Z.; Tóth, G.; Nyulasi, B.; Simig, G.; Volk, B. **Synthesis of 4-methyl-2*H*-1,2,3-benzothiadiazine 1,1-dioxides and their further transformation *via* alkylation and reduction steps.** *Synthetic Communications* **2019**, *49*, 3475–3485. DOI: 10.1080/00397911.2019.1673777. IF[2019]: 1.796. (contribution: 70%)

[P4] Gyűjtő, I.; Simig, G.; Porcs-Makkay, M.; Volk, B. **Synthesis and Chemistry of 1,2,3-Benzothiadiazine 1,1-Dioxide Derivatives: A Comprehensive Overview.** *Chemistry* **2020**, *2*, 674–690. DOI: 10.3390/chemistry2030043. (contribution: 100%)

[P5] Gyűjtő, I.; Porcs-Makkay, M.; Várda, E. F.; Pusztai, G.; Tóth, G.; Simig, G.; Volk, B. **Transformation of 2*H*-1,2,3-benzothiadiazine 1,1-dioxides variously substituted at the aromatic ring, *via* nucleophilic substitution and demethylation reactions.** *Synthetic Communications* **2020**, *50*, 3413–3423. DOI: 10.1080/00397911.2020.1801748. IF[2019]: 1.796. (contribution: 70%)

[P6] Gyűjtő, I.; Porcs-Makkay, M.; Szabó., G.; Kelemen, Z.; Pusztai, G.; Tóth, G.; Dancsó, A.; Halász, J.; Simig, G.; Volk, B.; Nyulászi, L. **Basicity-Tuned Reactivity: *diaza*-[1,2]-Wittig versus *diaza*-[1,3]-Wittig Rearrangements of 3,4-Dihydro-2*H*-1,2,3-benzothiadiazine 1,1-Dioxides.** *The Journal of Organic Chemistry* **2021**, *86*, 1685–1700. DOI: 10.1021/acs.joc.0c02512. IF[2019]: 4.335. (contribution: 70%)

Oral and poster presentations related to the PhD thesis

Porcs-Makkay Márta, Gyűjtő Imre, Simig Gyula, Volk Balázs: **A 3,4-dihidro-2*H*-1,2,3-benzotiadiazin-1,1-dioxid származékok átrendeződési reakciói.** *MTA Heterociklusos és Elemorganikus Kémiai Munkabizottság ülése, Balatonszemes, 2016.05.18–20*. (contribution: 100%, oral)

Gyűjtő Imre, Porcs-Makkay Márta, Lukács Gyula, Pusztai Gyöngyvér, Komáromi Anna, Nyulászi László, Simig Gyula, Volk Balázs: **Eljárás 4-szubsztituált 2*H*-1,2,3-benzotiadiazin-1,1-dioxidok előállítására**. *MTA Heterociklusos és Elemorganikus Kémiai Munkabizottság ülése, Balatonszemes, 2018.06.06–08*. (contribution: 70%, oral)

Gyűjtő, I.; Porcs-Makkay, M.;, Lukács, G.; Pusztai, G.; Simig, G.; Nyulászi, L.; Volk, B. **Synthesis of 4-substituted 2*H*-1,2,3-benzothiadiazine 1,1-dioxides starting from phenones.** *22nd International Conference on Organic Synthesis, Florence, Italy, 2018.09.16–21*. (contribution: 70%, poster)

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