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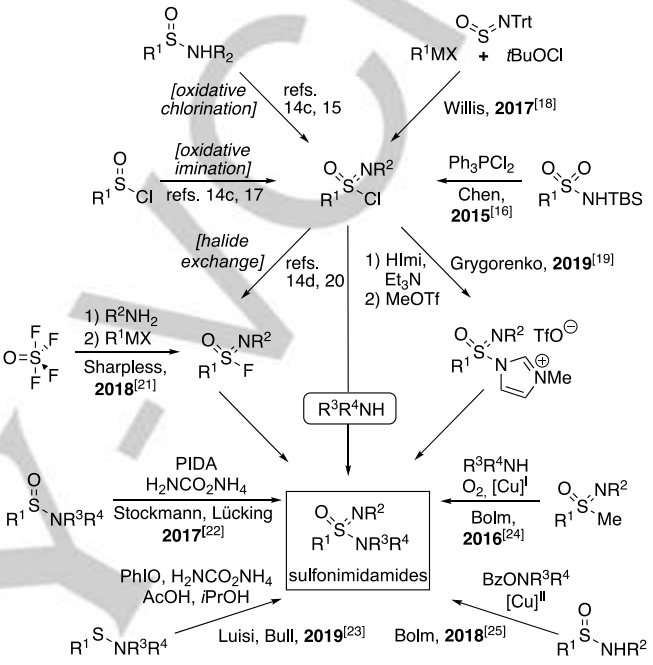
Additions to *N*-Sulfinylamines as an Approach for the Metal-free Synthesis of Sulfonimidamides: *O*-Benzotriazolyl Sulfonimidates as Activated Intermediates

Maximilian Bremerich, Christian M. Conrads, Tim Langletz, and Carsten Bolm*

Abstract: Sulfonimidamides are obtained in moderate to very good yield from *O*-benzotriazolyl sulfonimidates, which are key intermediates formed by reacting aryldiazonium tetrafluoroborates, *N*-tritylsulfinylamine, and *N*-hydroxybenzotriazole hydrate, mediated by a tertiary amine. The latter transformation proceeds in inexpensive and environmentally benign dimethyl carbonate as solvent, it does not require anhydrous conditions, and the product yields are generally exceeding 70%. The substrate scope is broad, and a wide range of sensitive organic functionalities is well tolerated. Probably, the reactions proceed via aryl radicals formed from diazonium cations with assistance by both the tertiary amine and the sulfinylamine.

Introduction

Sulfonamides are among the most abundant and important structural motifs in current medicinal and agricultural chemistry. They have a rich history in medical circles with, for example, sulfonamides being one of the first commercial antibiotics ever available.[1] Furthermore, sulfonamide derivatives have exhibited high biological activities including antiproliferal,[2] diuretic,[3] antihypertensive,[4] hypoglycemic,[5] antiinflammatory,[6,7] antiviral,[8] and herbicidal properties.[9] A recent report states the prevalence of the sulfamoyl group in sulfur-containing drugs to be as high as 29%.[10] Among the various sulfonamide derivatives, their monoaza-analogs, known as sulfonimidamides, have recently attracted increasing attention, in particular, because they are regarded as bioisosters of the parent compounds.[11,12] However, to date, only relatively few methods for the preparation of sulfonimidamides have been reported, most of them still having severe synthetic disadvantages preventing easy access to a wide variety of such attractive compounds.[13] Most sulfonimidamide syntheses proceed *via* sulfoximinoyl chlorides as reactive intermediates (Scheme 1), which are commonly not isolated because of their sensitivity to hydrolysis and redox side reactions.[14] In these protocols, key steps are oxidative chlorinations[14c,15,16] and/or iminations[14c,17] of lower-valent sulfur compounds, and subsequent nucleophilic substitutions of the resulting sulfoximinoyl chlorides. However, the employment of the strong oxidation or halogenation agents are often incompatible with sensitive functionalities and pose a risk in itself. In part, that is also true for the redox neutral approach introduced by Chen and Gibson, who used triphenylphosphine dichloride for the deoxychlorination of sulfonamides.[16] Functional-group sensitivity is also an issue when highly basic and nucleophilic organometallic reagents are applied as demonstrated by Willis and coworkers,[18] because they do not only require strictly anhydrous and/or otherwise inert conditions, but also do not tolerate important functional groups such as carbonyl groups of esters, ketones and aldehydes. Grygorenko and coworkers fine-tuned the stability of the reactive intermediates by the conversion of the sulfoximinoyl chlorides to the corresponding *N*-methylimidazolium triflates.[19] The same can be achieved by the involvement of the relatively stable fluorine-containing counterparts. While their preparation from sulfoximinoyl chlorides by halide exchange has long been known,[14d, 20] they can now directly be accessed by Sharpless' SuFEx approach.[21] Unfortunately, the practicability of this process is limited by the use of thionyl tetrafluoride (SOF_4), which is a toxic and corrosive gas. Stockmann, Lücking and coworkers could overcome many of the aforementioned challenges by directly converting sulfinamides to sulfonimidamides by oxidative imination with *in situ*-generated iminoiodinane(III) species.[22] Recently, this chemistry was extended by Luis, Bull and coworkers, who applied sulfenamides as starting materials.[23] Two very different approaches circumventing the formation of hydrolytically sensitive intermediates were introduced by us. Both were copper-



Scheme 1. Overview on approaches towards sulfonimidamides (Trt = trityl).

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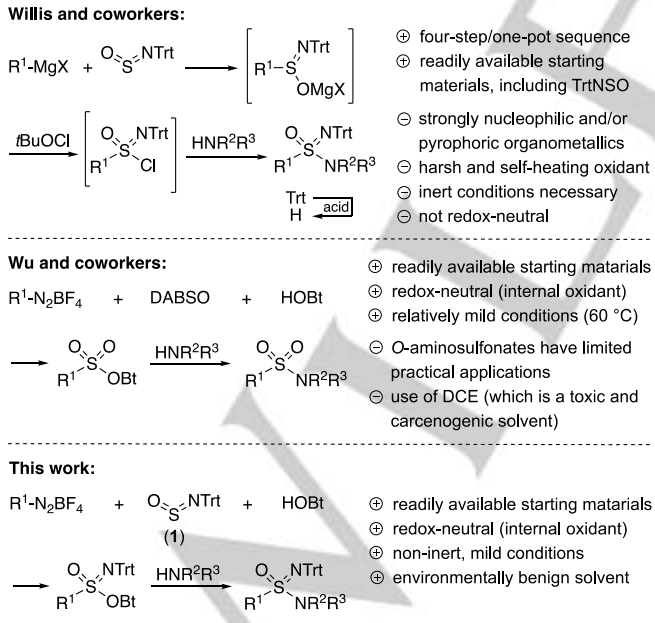
catalyzed. The first one involved oxidative dealkylations of *N*H-*S*-aryl-*S*-alkyl sulfoximines in the presence of secondary amines, which led to tertiary *N*H-sulfonimidamides, presumably via *S*-centered sulfoximinoyl radicals.[24] In the second, fully substituted sulfonimidamides were obtained by the reaction of *S*-arylsulfinamides with *O*-benzoyl hydroxylamine derivatives.[25] Due to the limits of the current methods, we were interested in devising a new approach towards sulfonimidamides, which should be flexible and showing a high functional group tolerance.

Results and Discussion

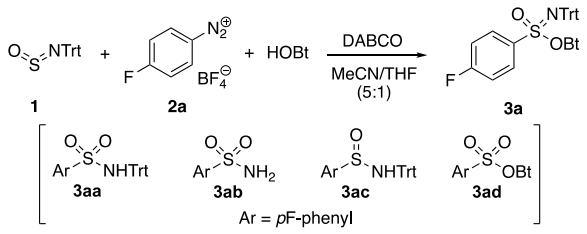
In 2017, Willis and co-workers reported groundbreaking findings on a one-pot-four-step reaction sequence (Scheme 2, top)[18,26] allowing the preparation of sulfonimidamides by addition of hetero)aryl- or alkylmagnesium halides to the hydrolytically stable and easily accessible reagent *N*-tritylsulfinylamine (**1**) followed by oxidation of the resulting sulfinimidate salts with *tert*-butylhypochlorite to give the corresponding sulfoximinoyl chlorides. Subsequent treatment of the latter products with primary and secondary amines yielded *N*-tritylsulfonimidamides, which were deprotected with strong acids to give *S*-aryl and *S*-alkyl-*N*H-sulfonimidamides in high yields. The redox cascade, in which the oxidation number of sulfur changed from +IV to +II back to +IV, was particularly conspicuous here. We also felt attracted by a report by Wu and coworkers (Scheme 2, middle),[27] who described the formation of sulfonamides via *O*-aminosulfonates, which were obtained from diazonium tetrafluoroborates, the solid sulfur dioxide surrogate DABSO (DABCO·2SO_2), and *N*,*N*-disubstituted hydroxylamines including 1-hydroxybenzotriazole (HOBt). The proposed reaction mechanism included a DABCO-assisted extrusion of molecular nitrogen from the diazonium salt, yielding an aryl radical and the DABCO-radical cation. The former attacked the SO_2 to form a sulfur-centered sulfonyl radical, while the latter abstracted a hydrogen atom from the hydroxylamine, forming the DABCO cation and an oxygen-centered hydroxylamine radical. Finally, combinations of both radicals gave the *O*-aminosulfonates in a remarkably exergonic process. If 1-hydroxybenzotriazole (HOBt) was employed as hydroxylamine, the methodology allowed the one-pot formation of sulfonamides by substitution with primary or secondary amines being present in the reaction mixture. A similar mechanism was reported for the formation of sulfonamides from aryl diazonium salts, DABSO, sodium azide and triphenylphosphine.[28] Considering **1** as protected monoaza-analog of SO_2, we wondered about its use for the synthesis of *O*-aminosulfonimidates and sulfonimidamides (Scheme 2, bottom). The realization of this strategy is reported here.



Scheme 2. Approach towards sulfonimidamides reported by Willis and co-workers (top), syntheses of *O*-aminosulfonates and sulfonamides described by Wu and co-workers (middle), and the fundamentals of the reaction sequence reported here (bottom).

With the intention to use a representative starting material that could be easily detected and followed by NMR spectroscopy, the study was initiated by applying 4-fluorophenyldiazonium tetrafluoroborate (**2a**) as aryl source. To our delight, **2a** reacted with equimolar amounts of *N*-tritylsulfinylamine (**1**) and HOBt hydrate in acetonitrile as hypothesized affording the targeted *O*-Bt-*N*-Trt-sulfonimidate **3a** in 42% yield. The reaction occurred within seconds, as revealed by the rapid termination of the nitrogen evolution. Varying the amount of DABCO (Table 1; with a 5:1 mixture of MeCN and THF as solvent for 20 min at ambient temperature; analysis by ^{19}F qNMR spectroscopy) showed that it acted as mediator and that at least one equivalent of this base had to be added to achieve high conversion of **2a** (>95%) providing **3a** in 60% yield (Table 1, entry 5). With less DABCO (Table 1, entries 1 and 3-4) or in the presence of $CaCO_3$ instead of DABCO (Table 1, entry 6) the product formation was not more

Table 1: Influence of the amount of DABCO on the conversion of diazonium salt **2a** and the yield of sulfonimidate **3a**.[a]



Entry	DABCO (equiv)	Conversion of **2a** [%][b]	Yield of **3a** [%][b]
1	0	22	20
2	**1.10**	**>95**	**60**
3	0.55	88	43
4	0.10	26	15
5[c]	0.10	23	17
6[d]	0.55	>95	0

[a] Performed at room temperature for 20 min. [b] Determined by ^{19}F qNMR with 3,3'-bis(trifluoromethyl)benzophenone as internal standard. [c] Use of $CaCO_3$ (1.10 equiv) in addition to DABCO. [d] Performed at 60 °C.

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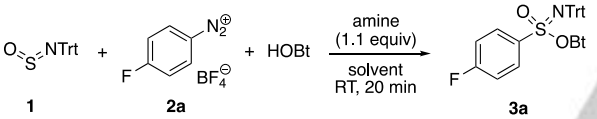
efficient.[29] Performing the reaction at 60 °C yielded *N*-tritylsulfonamide **3aa** as the main product (Table 1, entry 6). Other detectable side products were detritylated sulfonamide **3ab**, *N*-trityl-sulfinamide **3ac,** and *O*-Bt-sulfonate **3ad** (for details see the Supporting Information).

Screening various tertiary amines (Table 2) showed that *N*-methylpiperidine was superior over DABCO providing **3a** in a slightly higher yield (Table 2, entry 1 versus entry 7). Also triethylamine and DIPEA gave **3a** as the main product, but the yields were lower (Table 2, entries 2 and 3). Unexpectedly, tritylated sulfonamide **3aa** was preferentially formed with quinuclidine, pyridine, and DMAP (Table 2, entries 4-6).

The investigation of solvent systems revealed that both acetone and dimethyl carbonate (DMC) were significantly better than MeCN or the MeCN/THF mixture used before and that both were equally suitable if applied as single component solvent (Table 2, entries 7-10). A 1:1 mixture of both was not more effective (Table 2, entry 11). On the basis of these results and in light of the "green" solvent properties (non-toxic, water-immiscible and environmentally benign),[30] DMC was selected as medium for the subsequent studies.

Table 2: Base and solvent screening.

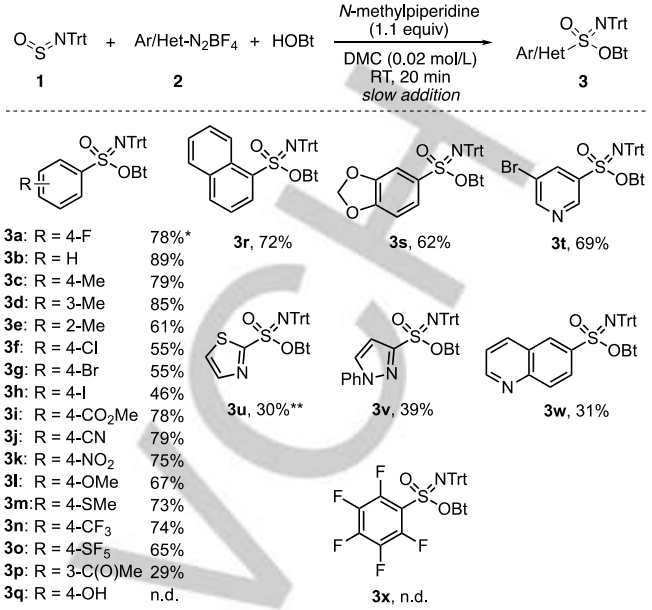


1 **2a** **3a**

Entry	Amine	Solvent	Yield of **3a** [%][a]
1	DABCO	MeCN/THF 5:1	60
2	Et_3N	MeCN/THF 5:1	47
3	DIPEA	MeCN/THF 5:1	44
4	quinuclidine	MeCN/THF 5:1	19[b]
5	pyridine	MeCN/THF 5:1	36[b]
6	DMAP	MeCN/THF 5:1	8[b]
7	*N*MePip	MeCN/THF 5:1	64
8	*N*MePip	MeCN	41
9	*N*MePip	Acetone	>95
10	***N*MePip**	**DMC**	**>95**
11	*N*MePip	Acetone/DMC 1:1	95

[a] Determined by ^{19}F qNMR spectroscopy with 3,3'-bis(trifluoromethyl)benzophenone as internal standard. [b] Tritylated sulfonamide **3aa** was the main product.

As expected for a radical reaction, the presence of dioxygen diminished the yield, whereas a large excess of water did not. Furthermore, the reaction proved sensitive to scale, concentration of the reactants, and addition sequence. Thus, a 10-fold increase in scale (from the initially used 0.05 mmol to 0.5 mmol) reduced the yield of **3a** from >95% to 63% (as determined by ^{19}F qNMR spectroscopy). A closer inspection revealed that the order in which the reactants were added was important. Hence, if a solution of HOBt hydrate and *N*-methylpiperidine in DMC was added dropwise to a suspension of **1** and **2a** (0.1 mmol/L) in the same solvent, a spectroscopic yield of **3a** of 77% was observed. Inverting the addition mode



Scheme 3. Substrate scope using various diazonium salts (* 73% yield on a 10 mmol scale; ** use of an undried diazonium salt with a purity of ca. 85%; n.d. = not detected).

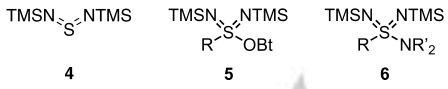
gave **3a** in only 56%. The importance of a carefully adjusted reactant concentration became even more apparent when the diazonium salt concentration was further changed from the commonly used 0.1 mol/L to either 0.5 mol/L or 0.02 mol/L. In those cases, **3a** was isolated in 46% and 69% yield, respectively. Degassing the solvent led to **3a** in 78% yield (at a concentration of 0.02 mol/L). Drying the solvent prior to use had no effect. Those final conditions proved robust for a scale-up leading to 73% of **3a** (after column chromatography) on a 10 mmol scale.

With the optimized conditions in hand, the substrate scope was investigated (Scheme 3). Pleasingly, the reaction conditions were applicable to a wide range of diazonium salts. Thus, phenylsulfonimidate **3b** was isolated in 89% yield. Methyl substituents in *para* or *meta* position of the aryl group reduced the yield of the corresponding sulfonimidate (**3c** and **3d**, respectively) slightly. More significant was the effect of an *ortho*-methyl group, which led to product **3e** in only 61% yield. In the series of compounds with *para*-halo substituents, the yields of **3a**, **3f**-**h** dropped with increasing atomic number of the halogen atom. This may be due to the fact that the halogen-bonding affinity of aryl halides increases with increasing polarizability from fluorine to iodine,[31] and therefore halogen-bonding effects between the nitrogen of one diazonium cation and the halogen substituent of another may lead to undesired coordination and thus to side reactions. This already suggests that electrostatic interactions play a role in the product formation, a hypothesis that was later substantiated in control experiments.

As generally expected in radical reactions, electronic effects had only a minor impact. Thus, diazonium salts with both electron-donating and -withdrawing substituents reacted well providing the corresponding sulfonimidates **3i**-**o** in yields ranging from 65% (for **3o** with a *para*-SF_5 group) to 79% (for **3j** with a *para*-CN substituent). Surprisingly, acetyl-containing product **3p**

was only obtained in 29% yield. Due to lack of reactivity of diazonium salts **2q** (bearing a free phenolic OH-group) and **2x** (containing a pentafluorophenyl moiety), sulfonimidates **3q** and **3x** remained inaccessible. In contrast, diazonium salts **2r** and **2s** with fused arenes reacted well providing 1-naphthyl or benzo[d][1,3]dioxol-5-yl derivatives **3r** and **3s** in yields of 72% and 62%, respectively. For heteroaromatic sulfonimidates, the yields strongly diverged, and the individual nature of the heterocycle appeared to play a role. Thus, while 3-bromopyridin-5-ylsulfonimidate **3t** was obtained in 69% yield, thiazol-2-yl, 3-phenylpyrazol-1-yl, and quinolin-6-yl derivatives **3u**-**w** were only formed in the 30% yield range. At least in part, the latter results might be due to chemical instabilities of the diazonium salts, as particularly observed for **2u**, which decomposed at temperatures above –10 °C during its synthesis.

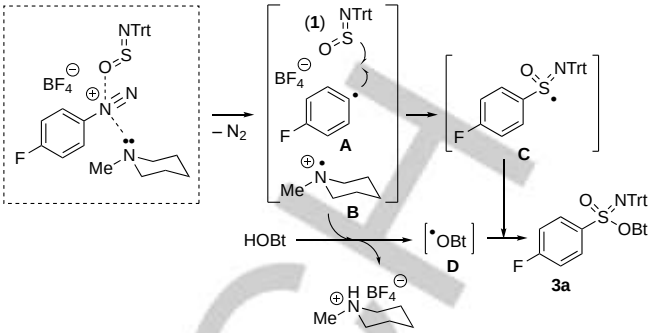
With the goal to shine light into the reaction mechanism, various control experiments were performed. First, the reaction between **1** and **2a** was performed in the absence of additional base. Also in MeCN (for the result with a 5:1 mixture of MeCN and THF a solvent, see Table 1, entry 1), product **3a** was obtained in low yield (15%) after 1 h at ambient temperature indicating the critical role of the tertiary base. When the reaction was performed in the presence of two equiv of TEMPO as radical scavengers, the formation of **3a** was completely suppressed suggesting the intermediacy of radicals as key components. Trapping of such radical by 4-phenylstyrene (instead of HOBt) proved impossible. Attempts to substitute *N*-tritylsulfinylamine (**1**) by bis(trimethylsilyl)sulfur diimide (**4**) in the coupling with **2a** targeting a representative of the virtually unknown arylsulfondiimidates (**5**) and arylsulfondiimidamides **6**[14d,32] remained unsuccessful (Figure 1). No reaction occurred indicating the importance of the oxygen in reagent **1**. Neither the reaction of **2a** with **1** and HOBt nor the analogous one with **4** instead of **1** were catalyzed by the addition of copper(I) chloride (10 mol %) intending to promote a Sandmeyer-type coupling reaction via radicals.



4 **5** **6**

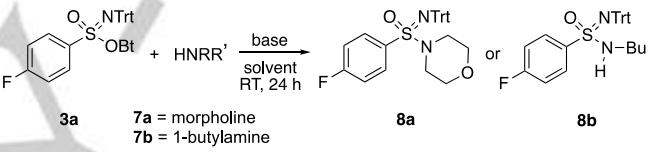
Figure 1. Relevant compounds in the control experiments.

The aforementioned observations lead us to propose the mechanistic scenario depicted in Scheme 4. In a highly organized (transition) state, both the tertiary amine and sulfinylamine **1** coordinate to the nitrogen of the diazonium salt. Upon electron transfer from the tertiary amine to give radical cation **B**, dinitrogen is expelled and aryl radical **A** is formed. Being close to **1**, aryl radical **A** adds to the sulfur reagent to give sulfoximiminoyl radical **C**. Hydrogen abstraction from HOBt by radical cation **B** generates BtO radical **D** and the HBF_4 salt of the tertiary amine. In an exergonic process, which provides the driving force of the process, combination of radicals **C** and **D** leads to product **3a**.



Scheme 4. Mechanistic proposal.

The isolated *N*-trityl-*O*-Bt sulfonimidates **3** were white to yellowish solids that could be purified by conventional flash column chromatography in air at room temperature. The decomposition rate on silica is low, and they can be stored at –18 °C over months without significant signs of degradation, rending them highly attractive as intermediate in subsequent synthetic applications. Here, we developed their use in the preparation of sulfonimidamides **5** (Scheme 5).



3a **7a** = morpholine, **7b** = 1-butylamine **8a** **8b**

Scheme 5. Conversion of sulfonimidate **3a** to sulfonimidamides **8a** and **8b** by reaction with morpholine (**7a**) or 1-butylamine (**7b**), respectively.

For the initial optimization, morpholine (**7a**) and 1-butylamine (**7b**) were selected as representative nucleophiles. To our delight, both reacted well with sulfonimidate **3a**, provided that an additional base was added and that acetonitrile was applied as solvent. Thus, for morpholine, sulfonimidamide **8a** was obtained in up to 77% yield (as determined by ^{19}F qNMR spectroscopy), and **8b**, stemming from 1-butylamine, was formed in 86% yield. As additional bases, *N*-methylpiperidine and triethylamine were applied, respectively. Attempts to use other solvents than acetonitrile (DMC, acetone, DMF or pyridine) led to lower conversions and yields. In the reaction of **3a** with 1-butylamine (**7b**), triethylamine could be substituted by potassium carbonate without affecting the yield of **8b**. Adding catalytic amounts (10 mol %) of potassium iodide or DMAP, which are known catalysts for the aminolysis of methyl esters,[33] to a mixture **3a** and **7b** did not improve the yield **8b**. Noteworthy, the protocol did not require dry conditions, and hydrolysis products remained undetected.

Scheme 6 summarizes the results of the substrate scope evaluation in reactions with **3a**. As additional base, 1 equiv of triethylamine was used in acetonitrile for 24 h at ambient temperature. The nucleophile quantities were 2 equiv for primary amines and 1.2 equiv for secondary amines. Most reactions proceeded well affording the targeted sulfonimidamide **8** in good yields. In the series of primary amines, ethyl-, *iso*-propyl-, and benzyl amines led to the corresponding products **8d**-**f** in yields of 79%, 75%, and 71%, respectively. Applying methylamine (**7c**) proved less effective under the standard reaction conditions,

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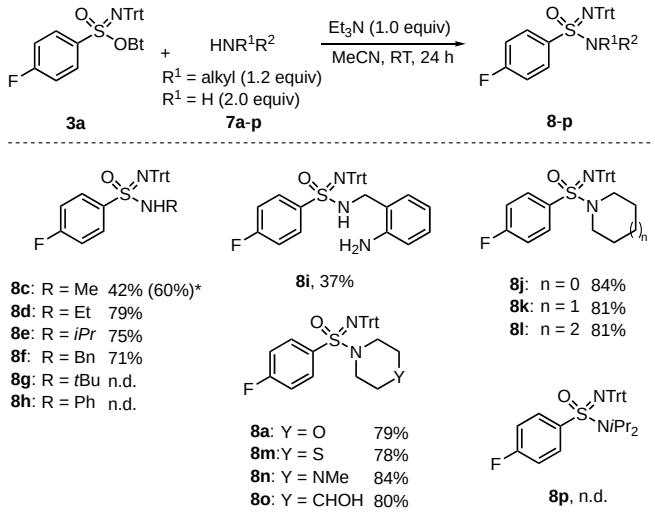
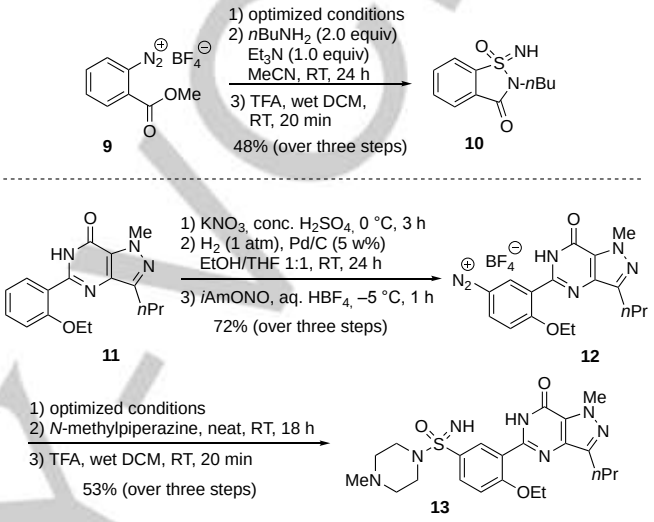


Scheme 6. Conversion of sulfonimidate **3a** to sulfonimidamides **8** (* use of a large excess of the nucleophile; see text for details).

giving **8c** in only 42% yield. This result could be improved by carrying out the substitution in an 8 M ethanolic solution of methylamine (corresponding to an excess of about 28 equiv), which led to **8c** in 60% yield. Sulfonimidamides **8g** and **8h** remained inaccessible, presumably due to steric reasons in the case of *tert*-butyl amine (**7g**) and the low nucleophilicity for aniline (**7h**). Attempts to apply **7h** in DMF instead of MeCN, at higher temperatures, or after prior deprotonation with sodium hydride, remained unsuccessful. Considering that benzyl amine (**7f**) reacted well to give **8f** while aniline (**7h**) was inactive, 2-aminobenzylamine (**7i**) containing both a benzylic and an anilinic nitrogen, was applied. As hypothesized, the reaction with **3a** was chemoselective providing sulfonimidamides **8i** in 37% yield. Alicyclic amines reacted almost uniformly providing products in yields of about 80%. As revealed by the results for sulfonimidamides **8j-l** stemming from reactions with pyrrolidine (**7j**), piperidine (**7k**) and azepane (**7l**), the ring size had no significant influence. Besides morpholido sulfonimidamide **8a**, thiomorpholido and *N*-methylpiperazido sulfonimidamides **8m** and **8n** could be prepared, and again the yields of all products in this series were in the 80% range. Particularly noteworthy is the 80% yield in the formation of sulfonimidamide **8o** derived from **3a** and 4-hydroxypiperidine (**7o**) as it revealed a strong reactivity preference of the *N*- over the *O*-nucleophilic site of the bifunctional amine. This pronounced chemoselectivity is not only of synthetic interest but also explains the observed high resistance of the sufonimidates towards hydrolysis. The employment of other nucleophiles (thiolate, fluoride, and azide) led to product mixtures, in which only the corresponding sulfinamide (4-fluoro-*N*-tritylbenzenesulfinamide) could be identified.

In order to prove the practicability of the new sulfonimidamide synthesis, two analogs of pharmacologically relevant sulfonamides were prepared (Scheme 7). First, endo-*N*-*n*-butyl-substituted azasaccharine derivative **10** was obtained from 2-carboxymethylphenyldiazonium tetrafluoroborate **9** with a total yield of 48% over three steps. This product was of interest, because Chen and co-workers had shown that saccharine aza bioisosters such as compounds of type **10** exhibited promising preclinical properties.[34] The second molecule in this series was an analog of sildenafil, which is a commercial PDE5 inhibitor with a sulfonamide core. Diazonium salt **12** was prepared in an overall yield of 72% over several steps from the commercially available **11**. Using the aforementioned optimized conditions for the sulfonimidate formation followed by treatment with *N*-methylpiperazine and acidic deprotection of the trityl group, **11** was converted to sulfonimidate **13** in 53% yield over three steps.



Scheme 7. Syntheses of two analogs of pharmacologically relevant sulfonamides.

Conclusion

We introduced new protocols for mild preparations of activated sulfonimidates and sulfonimidamides. First, aromatic or heteroaromatic diazonium salts are reacted with the bench-stable reagent *N*-tritylsulfinylamine (**1**) and 1-hydroxybenzotriazole hydrate in the presence of *N*-methylpiperidine to give a broad range of *N*-trityl-*O*-benzotriazolylsulfonimidates **3**. Non-toxic, environmentally benign dimethyl carbonate is the solvent. The reaction takes place at room temperature without the requirement of dry conditions. Degassing of the solvent and a low reactant concentration have beneficial effects on the yields, but both are not critical for the success of the transformations. Many functional groups are tolerated, and electronic effects of substituents have only a minor effect of the product yields. In a subsequent step, the sulfonimidates **3** can be converted to the corresponding sulfonimidamides **5** by simple reactions with primary or secondary amines, whereby only aliphatic amines react. This chemoselectivity is without precedent. The formation of the sulfonimidates probably takes place by a radical mechanism involving pre-organized aggregates of the reactants. A novel azasaccharine derivate and an unprecedented sulfonimidamide analog of sildenafil have been prepared using the aforementioned methodologies.

Acknowledgements

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Keywords: Diazonium salts • *N*-hydroxybenzotriazole • sulfonimidamide • sulfonimidates • *N*-tritylsulfinylamine

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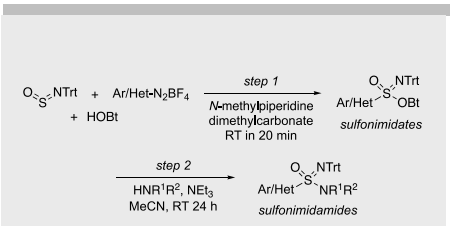

N-Tritylsulfinylamine, aryldiazonium tetrafluoroborates, and *N*-hydroxybenzotriazole hydrate react to give *O*-benzotriazolyl sulfonimidates, which can be converted to sulfonimidamides in good yields. The two processes are mild, allowing preparations of a wide range of functionalized products. The applicability was demonstrated by the syntheses of a novel azasaccharine derivate and a sulfonimidamide analog of sildenafil.

*Maximilian Bremerich, Christian M. Conrads, Tim Langletz, and Carsten Bolm**

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