COMMUNICATION

N-(2,3,5,6-Tetrafluoropyridyl)sulfoximines: Synthesis, X-Ray Crystallography, and Halogen Bonding

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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In the presence of KOH, *N*H-sulfoximines react with pentafluoropyridine to give *N*-(tetrafluoropyridyl)sulfoximines (*N*TFP-sulfoximines) in moderate to excellent yields. Either a solution-based or a superior solvent-free mechanochemical protocol can be followed. X-ray diffraction analyses of 25 products provided insight into the bond parameters and conformational rigidity of the molecular scaffold. In solid-state structures, sulfoximines with halo substituents on the *S*-bound arene are intermolecularly linked by C–X···O=S (X = Cl, Br) halogen bonds. For mixtures of three different *S*-pyridyl-substituted *N*TFP-sulfoximines and *N*-iodosuccinimide (NIS) in $CDCl_3$, association constants were determined by ^{1}H NMR spectroscopy. The data revealed a dependence of the halogen bond strength on the position of the pyridyl nitrogen indicating the presence of N–I···N(*S*-pyridyl) interactions. Neither the S=O oxygen nor the tetrafluoropyridyl-substituted nitrogen of the sulfoximine appeared to be involved in halogen bonding.

Introduction

Sulfoximines are valuable compounds in agrochemical,[1] medicinal,[2a-c] and pharmaceutical chemistry.[2d-j] Their importance has also been acknowledged in synthetic organic chemistry, where sulfoximines found numerous applications in asymmetric catalysis,[3a-d] auxiliary-based synthesis,[3e-g] and C–H bond functionalization.[3h,i] In many cases, *N*H-sulfoximines are key intermediates, as they can easily be modified at the sulfoximine nitrogen by alkylation,[4] arylation,[5] and vinylation,[5c,6] just to name a few relevant transformations. For preparative simplification and exploration, sulfoximidoyl-containing building blocks were introduced.[7,8]

The introduction of fluoro substituents into drug-like molecules and agrochemicals can tremendously affect the properties of the resulting compounds, for example, by decreasing their basicity and improving their bioavailability.[9] In the context of sulfoximine chemistry, N–C_F bond formations starting from *N*H-sulfoximines are of particular interest.[10] Up to date, only a few reactions of this type are known, including our contributions on (i) silver-catalyzed *N*-trifluoromethylations,[11] and (ii) direct copper-catalyzed coupling with polyfluoroarenes leading to products with N–$C_{aryl\text{-}F}$ bonds.[12]

In 2019, Brittain and Cobb introduced the tetrafluoropyridyl (TFP) group for the protection of phenols.[13a] TFP was easily installed and proved cleavable under mild reaction conditions. Subsequently, the same authors showed that TFP-protected phenols revealed a unique regioselectivity in electrophilic aromatic substitution reactions due to the pronounced electron-withdrawing property of the protecting group.[13b] Inspired by these reports, we wondered about the applicability of the TFP group in the context of sulfoximine chemistry. Besides the expected synthetic benefits, we also noted that the first step of the intended protocol involved the formation of a new N–$C_{aryl\text{-}F}$ bond by an hitherto unprecedented S_NAr pathway.[14] In light of our previous studies related to alkylations of deprotonated *N*H-sulfoximines,[15] this coupling was anticipated to be nontrivial. Finally, an interesting structural aspect of *N*-(tetrafluoropyridyl)-sulfoximines was identified: Considering the high degree of fluorination of the *N*-tethered pyridyl group, halogen bonding with suitable donors could occur opening attractive opportunities in crystal design and engineering.[16] Seeing an array of potential applications of halogen-bonded sulfoximine-based Active Pharmaceutical Ingredients (APIs) it is surprising that, to the best of our knowledge, such questions have yet remained unaddressed in sulfoximine chemistry. Here, we report our attempts to shine a light on the various facets of this appealing synthetic niche with high potential.[17]

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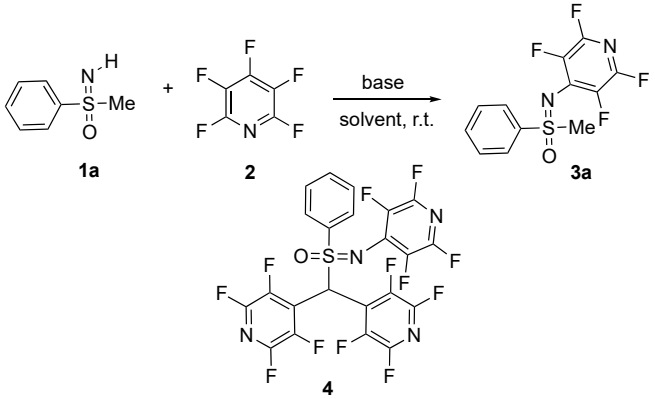
†Electronic Supplementary Information (ESI) available: CCDC 2027276 –2027300, 2027322. For ESI and crystallographic data in CIF See DOI: 10.1039/x0xx00000x

Results and Discussion

Development of synthetic protocols

For the initial process development and optimization, *N*H-*S*-methyl-*S*-phenylsulfoximine (**1a**), which can easily be obtained by standard routes as racemate or enantiopure compound,[18] was selected as representative starting material. The attempt to directly react **1a** in acetonitrile with pentafluoropyridine (**2**) remained largely unsuccessful affording only traces of the expected product **3a** (Table 1, entry 1). Apparently, the *N*H-sulfoximine was not nucleophilic enough to initiate the intended S_NAr process.[19] With K_2CO_3 as base as used by Brittain and Cobb in their system for phenol-protection,[13] **3a** was obtained in 9% yield. At a higher concentration, the yield of **3a** was 18% (Table 1, entries 2 and 3). The subsequent base screening showed that the organic bases DABCO and NEt_3 were ineffective providing only traces of **3a** (Table 1, entry 4, and Table S2 in the Supporting Information). In contrast, inorganic bases significantly improved the reaction yields of **3a**. Thus, with K_3PO_4, NaOH, and KOH **3a** was obtained in 36%, 24%, and 78% yield, respectively (Table 1, entries 5-7). Apparently, the size of the cation as well as the shape and geometry of the anion impacted the reaction outcome.[20]

Table 1 Optimization of reaction conditions for the synthesis of 3a in solution[a]



1a + **2** → **3a**; **4**

Entry	Base [equiv.]	Solvent [mL]	**3a** [%]
1	–	MeCN (2.50)	trace [b]
2	K_2CO_3 (3.00)	MeCN (2.50)	9
3	K_2CO_3 (3.00)	MeCN (0.50)	18
4	DABCO (3.00)	MeCN (0.50)	trace
5	K_3PO_4 (3.00)	MeCN (0.50)	36
6	NaOH (3.00)	MeCN (0.50)	24
7	KOH (3.00)	MeCN (0.50)	78
8	KOH (3.00)	Toluene (0.50)	79
9	KOH (3.00)	EtOH (0.50)	45
10	**KOH (3.00)**	**THF (0.50)**	**92 (96)** [c]
11	KOH (3.00)	DMSO (0.50)	88 [d]

[a] **1a** (0.30-0.50 mmol), **2** (1.50 equiv.), overnight (for more details, see SI). [b] use of 1.05 equiv. of **2**. [c] reaction time: 24 h. [d] formation of byproduct **4**, which could not fully be separated from **3a**.

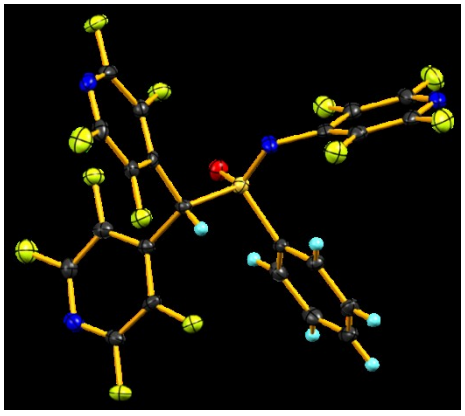


Fig. 1 X-ray crystal structure of product **4**.[24]

Because at this stage, the use of KOH in acetonitrile had led to the highest yield of **3a** (78%), this base was also applied in the subsequent solvent screening (Table 1, entries 7-11). While performing the reaction in toluene gave **3a** in a similar yield (79%) as in acetonitrile, the product formation was hampered in ethanol (45%). A significant improvement was observed with THF as solvent providing **3a** in 92% (Table 1, entry 10). This yield could even be raised further by extending the reaction time from overnight to 24 h leading to **3a** in 96% yield.[21] An interesting observation was made with the super-base combination of KOH in DMSO.[15,22,23] Compared to the reaction in THF, the yield of **3a** was almost the same (about 88%, Table 1, entry 11), but under those conditions an inseparable byproduct **4** was formed. After a significant analytical effort, **4** crystallized and its molecular structure was determined by X-ray crystal structure analysis.[24] As shown in Figure 1, three pyridyl units had been incorporated into **4**, one of which was located at the sulfoximine nitrogen, as expected, and the other two being linked to the sulfoximine carbon. Apparently, the super-basic system had led to a series of arylations including two at the former sulfoximine methyl. Interestingly, neither a mono- nor a tripyridyl/carbon-connected product was observed.[25]

At this stage of the investigation, a highly efficient procedure for linking the tetrafluoropyridyl group to the sulfoximine nitrogen had been developed providing *N*TFP-sulfoximine **3a** in up to 96% yield. Those results were highly motivating and challenged us to improve the reaction conditions even further. A recent discovery in our mechanochemical research made us optimistic.[26] While working on palladium-catalyzed carbonylations in ball mills we found that also an *N*H-sulfoximine could efficiently be addressed leading to the corresponding *N*-benzoyl derivative after coupling with phenyliodide.[26,27] Noteworthy, the reaction was solvent-free thereby avoiding the presence of any additional potentially hazardous reagent. Hypothesizing that this approach could also be beneficial here, we started investigating the reaction between **1a** and **2** under mechanochemical conditions in a mixer mill. As the results presented in Table 2 reveal, the solvent-free procedure for the *N*-arylation of **1a** with **2** showed parallels to the aforementioned solution-based process but differed in several important points. First, it also required the

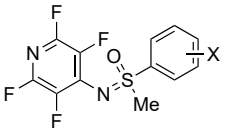
presence of base, and KOH proved optimal. Second, as in solution, a 1.5-fold excess of **2** over **1a**, and the use of 3.00 equiv. of KOH were essential for getting a high yield of **3a**, which finally reached a value of 90% under standard conditions (Table 2, entry 6). Third, the solvent-free reaction was much faster than the one in THF, allowing to isolate product **3a** in 92% yield after only 15 min (Table 2, entry 10). Fourth, no byproducts (such as **4**) were detected, and fifth, the fact itself that the reaction was solvent-free allowing to easily upscale the process (with 3.0 mmol of **1a**) leading to **3a** in a yield of 93%.

Table 2 Optimization of reaction conditions for a mechanochemical synthesis of **3a**[a,b]

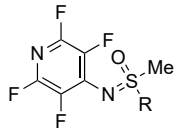
Entry	Equiv. of **2**	Base [equiv.]	**3a** [%]
1	1.50	–	trace
2	1.20	DABCO (1.05)	22
3	1.50	K_3PO_4 (3.00)	54
4	1.50	$LiOH·H_2O$ (3.00)	17
5	1.50	NaOH (3.00)	59
6	1.50	KOH (3.00)	90
7	1.20	KOH (1.05)	62
8	1.20	KOH (3.00)	74
9	1.50	KOH (1.50)	84
10	**1.50**	**KOH (3.00)**	**92** [c] **(93)** [c,d]

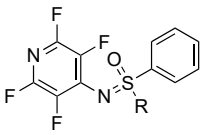
[a] Reaction conditions: Stainless steel milling jar (5 mL), 1 ball (7 mm) of the same material, 90 min, 25 Hz, **1a** (50 mg, 0.32 mmol). [b] For further details of the screening, see the Supporting Information. [c] After 15 min. [d] Use of 3.00 mmol of **1a**.

In light of the very positive results of the mechanochemical approach, the substrate scope was evaluated under those optimized conditions. Figure 2 summarizes the results.



3b: X = 4-F 71%
3c: X = 2-Cl 90%
3d: X = 3-Cl 72%
3e: X = 4-Cl 79%
3f: X = 2-Br 90%
3g: X = 3-Br 71%
3h: X = 4-Br 21%
3i: X = 4-I 63%
3j: X = 2-MeO 87%
3k: X = 4-MeO 75%
3l: X = 4-Me 78%
3m: X = 4-NO_2 31%





3n: R = 2-py 64%
3o: R = 3-py 50%
3p: R = 4-py 70%
(**3q**: R = 4-py-*N*-oxide 96%)
3r: R = 2-thiophenyl 54%
3s: R = Me 37%
3t: R = cyclohexyl 42%
3u: R = Ph 84%
3v: R = Bn 47%
3w: R = Et 81%
3x: R = *i*Pr 76%
3y: R = cyclopropyl 65%
(*R*)-**3a**: X = H 95%

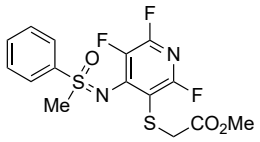
Fig. 2 Prepared *N*TFP-sulfoximines (under conditions shown in Table 2, entry 10 except for **3q**, which was obtained by oxidation of **3p** with *m*CPBA).

In general, sulfoximines with an *S*-methyl and a substituted *S*-aryl group reacted well providing the corresponding products (**3b**-**3m**) in good yields.[28] The only two exceptions were *N*H-sulfoximines **1h** and **1m** with a *para*-bromo and a *para*-nitro substituent at the arene, which led to **3h** and **3m** in only 21% and 31% yield, respectively. Because the other results did not indicate any significant steric or electronic impact of the aryl substituent on the TFP group introduction, we assume that in those two cases the lower product yields were due to a higher degree of crystallinity of the starting materials compared to their close structural analogs. Related observations have been reported in metal-catalyzed cross coupling reactions.[29] In the series of *S*-methyl-*S*-pyridyl- substituted sulfoximines all three *N*TFP-protected derivatives **3n**-**3p** were formed, and the yields ranged from 50% to 70%. Product **3p** could be further functionalized by oxidation with *m*CPBA leading to *N*TFP-protected sulfoximine **3q** with an *S*-4-pyridyl-*N*-oxide substituent in 96% yield. Also *S*-methyl *N*H-sulfoximines with *S*-thiophenyl and additional *S*-alkyl substituents provided the desired products (**3r**-**3t**) from the reaction of the corresponding *N*H-sulfoximine with **2**, but in all three examples the yields remained moderate ranging from 37% (for *S*,*S*-dimethyl substituted derivative **3s**) and 54% (for the *S*-thiophenyl-containing product **3r**). The results for the formation of **3u**-**y** show that also *N*H-*S*-phenylsulfoximines with substituted *S*-alkyl groups reacted, providing the corresponding products in yields of 47% (for **3v**) to 84% (**3u**).

Applying enantioenriched *N*H-sulfoximine (*R*)-**1a** in the reaction with **2** led to 95% of (*R*)-**3a** with an enantiomeric ratio of 99:1 confirming that the mechanochemical *N*-protection had occurred without affecting the stereochemistry at sulfur.

On the basis of previous observations,[30] we expected the newly formed N–$C_{aryl\text{-}F}$ bond to be rather stable.[31,32] This hypothesis was tested by subjecting **3a** to a series of potential deprotection protocols. Starting with the one reported by Brittain and Cobb for the phenol regeneration from their TFP-protected counterparts using a mixture of methyl thioglycolate, KF, and 18-crown-6 in aqueous acetonitrile at elevated temperature led to no destruction of the N–$C_{aryl\text{-}F}$ bond, and the molecule remained intact. The only isolable product was a small amount (16%) of **5** resulting from a nucleophilic substitution of a 3-fluoro group at the *N*-pyridyl substituent by the applied thiol (Figure 3).[25]

Also, under various acidic, basic, reductive, oxidative, and photocatalytic conditions (for details see Table S8 in the



5

Fig. 3 Compound **5** obtained in 16% yield by treatment of **3a** with methyl thioglycolate, KF, and 18-crown-6 in aqueous acetonitrile at 50 °C.

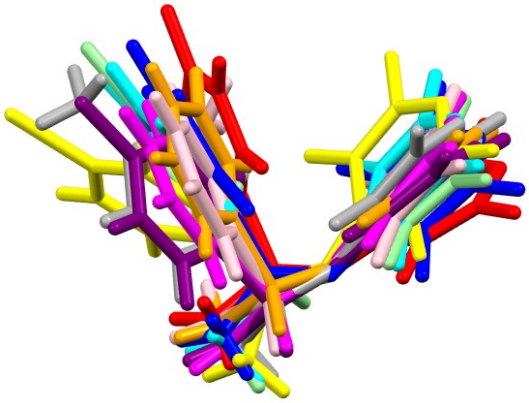


Fig. 4 An overlay structure of *N*TFP-sulfoximines **3a**, **3b**, **3c**, **3e**, **3f**, **3g**, **3h**, **3i**, **3j**, and **3l**.

Supporting Information) **3a** remained stable suggesting *N*TFP-sulfoximines as convenient building blocks for subsequent investigations and potential functionalizations of related scaffolds.

X-Ray Crystallography

A total of 25 *N*TFP-sulfoximines were crystallized and characterized by X-ray diffraction analysis. An overlay structure including 10 structures is shown in Figure 4.

The mean, N–C(TFP) [1.379 Å], S=N [1.543 Å], and S=O [1.445 Å] bond lengths in the *N*TFP-sulfoximines are in agreement with distances reported for N–C_F sulfoximines, where C_F is CF_3 and C_6F_5 (Figure 5).[10f,11] In solid-state X-ray structures, the typical N(sp^2)–C(sp^2) single bond distance is 1.40 Å.[33] The resonance interaction between p-electrons of N(sp^2) and π-electron clouds of C(sp^2) depends on the electron-donating and electron-withdrawing power of the π-groups attached to the N(sp^2)-atom. Such a phenomenon extends electron delocalization and induces a partial double bond character in N(sp^2)–C(sp^2) type systems. Here, the average N–C(TFP) bond distance is shorter by ~0.08 Å when compared to *N*Ph-sulfoximines, as in *N*C_6F_5-sulfoximines, suggesting a 'partial double bond' character of the N–C(TFP) bond. The pronounced chemical inertness of this bond supports this view. The electronic changes of the R^1 and the R^2 group, and molecular packing forces exerted on sulfur ONC_2 tetrahedra and other parts of *N*TFP-sulfoximines skeleton seems to play a minor role in governing the X-ray crystal structure bond parameters (for details, see Table S16 in the Supporting Information).

Halogen bonding

The investigation of halogen bonding involved two approaches: In the first, X-ray crystal structures data were used to identify interactions between halo-containing *N*TFP-sulfoximines in the solid state (Figures S32-38). The second approach involved solution ^{1}H NMR titrations to reveal intermolecular halogen

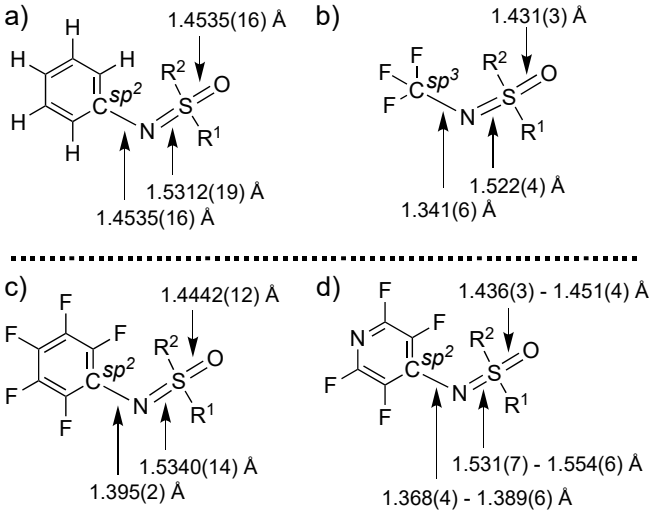


Fig. 5 Comparison of X-ray crystal bond distances in (a) an *N*Ph-sulfoximine, (b) an *N*CF_3-sulfoximine, (c) an *N*C_6F_5-sulfoximine, and (d) *N*TFP-sulfoximines.

bonds (XBs) between *S*-pyridyl-substituted *N*TFP-sulfoximines and NIS as complexing partner.

Examining the X-ray crystal structures of halogenated *N*TFP-sulfoximines **3b**-**i** revealed significant C–X···O=S interactions for compounds **3c** and **3f** (Figures 6a and 6b).[24] The corresponding distances of ca. 3.213 Å [∠C–Cl···O = 163.8°] and 3.169 Å [∠C–Br···O = 164.1°] were below the sum of the van der Waals radii of the interacting X- and O-atoms.[34] To our surprise, the behavior of *para*-iodo-substituted *N*TFP-sulfoximine **3i** was very different. In the molecular packing, it neither exhibited XB short contacts to an oxygen nor a nitrogen atom, but instead, the structure of **3i** was a dimer stabilized through C–I···π (ca. 3.531 Å) contacts (Figure 6c). Of interest is the position of the intermolecular contact, bringing the iodine close to the pyridine nitrogen.

N-Haloimides are known to be excellent XB-donors forming strong halogen bonds with *N*- and *O*-heterocycles, even in solution.[16,35] In light of the aforementioned XB solid-state interactions of halogenated *N*TFP-sulfoximines and noting the multiple sp^2 hybridized *O* and *N* atoms in such compounds, we presumed that combinations of *N*TFP-sulfoximines and *N*-haloimides e.g. *N*-iodosuccinimide (NIS) could also lead to XBs, here of the type $(CO)_2$N–I···O=S and $(CO)_2$N–I···N(TFP). To test this hypothesis, 1:1 mixture of NIS and **3a** in acetone-d_6 were analyzed by ^{1}H NMR spectroscopy.[35b] To our disappointment, the NIS protons showed the same chemical shift as for NIS alone indicating that no complexation had occurred. The same behavior was observed when acetone-d_6 was substituted by the XB non-competitive solvent $CDCl_3$. Presumably, both potential XB acceptor sites of **3a**, the TFP nitrogen and the sulfoximine oxygen, were too electron-deficient to allow a detectable binding to NIS in solution. The aforementioned '(TFP)C=N=S=O' delocalization (Figure 5) might play an important role in this scenario.

The situation changed when *S*-pyridylsulfoximines **3n**-**p** were tested in 1:1 combination with NIS. Now, a significant ^{1}H NMR chemical shift difference was observed in $CDCl_3$ for the NIS

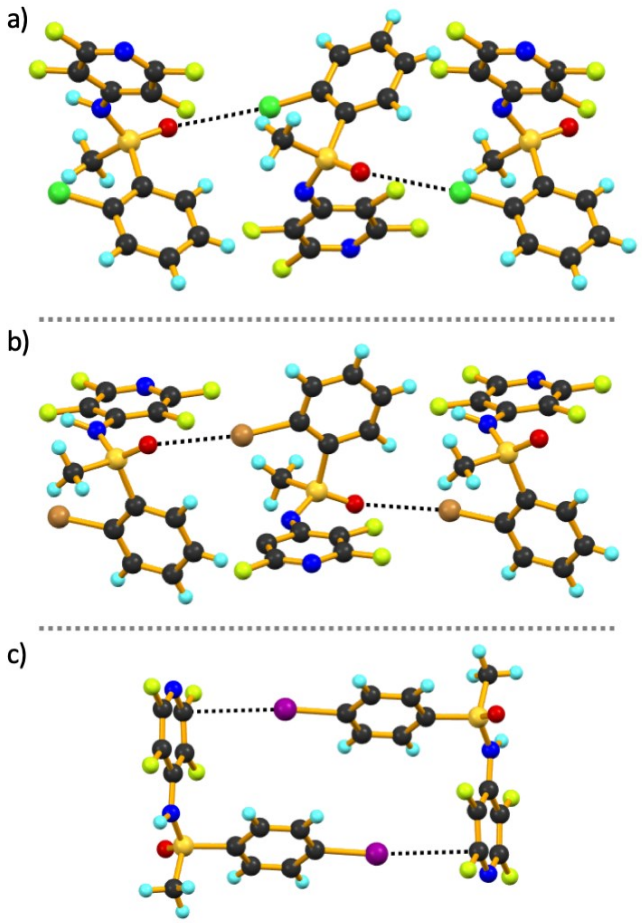


Fig. 6 Partial 1D polymeric halogen-bonded chain view of (a) **3c**, and (b) **3f**. (c) 1D Halogen-bonded dimer of **3i**. The black dotted lines represent C–Cl···O=S and C–Br···O=S XBs, and C–I···π interactions.[24]

protons compared to respective resonances of NIS alone, indicating halogen bonding interactions. With the intention to estimate association constants (K_a) for the *S*-pyridyl-based *N*TFP-sulfoximines and NIS, and to deduce the solution binding model of the corresponding XB-complexes ^{1}H NMR titration experiments were carried out. For following the XB complexation, the chemical shift changes of the NIS C–H protons were used, and K_a-estimates were obtained by applying the Bindfit online program (Figures S1-3 in the Supporting Information).[36] The resulting experimental K_a-values for NIS-**3n**, NIS-**3o**, and NIS-**3p** were 7.6 M^{-1}, 78.1 M^{-1}, and 112.5 M^{-1}, respectively. Considering the aforementioned results of the solution-based NIS binding attempts with **3a**, we assume that in these cases, the *S*-pyridyl nitrogen interacted with the XB donor (Figure 7). Thus, the lower K_a-value of NIS-**3n** can then be attributed to a weaker $(CO)_2$N–I···N(Py) halogen bond compared to the analogous complexes with **3o** and **3p** due to steric crowding. In this assumed 1:1 solution binding model, $(CO)_2$N–I···O=S and $(CO)_2$N–I···N(TFP) interactions appear insignificant.

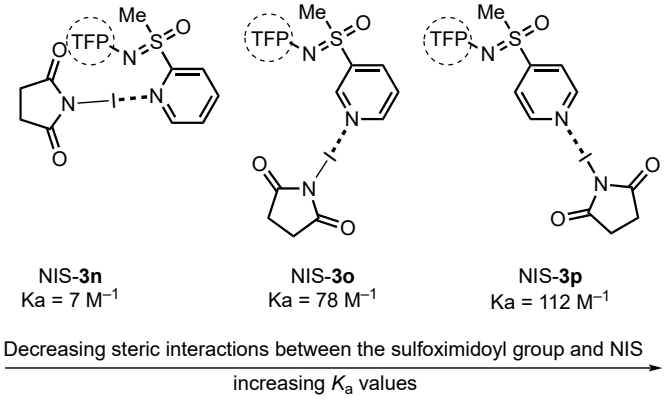


Fig. 7 Halogen-bonded complexes of NIS-**3n**, NIS-**3o**, and NIS-**3p**.

Conclusions

We have shown that *N*H-sulfoximines react with pentafluoropyridine by *N*-functionalization leading to *N*-(tetrafluoropyridyl)-sulfoximines in high yields. The process can be performed in solution or under mechanochemical conditions. Both require the presence of KOH, and the latter is significantly faster and less byproducts are formed. The products are chemically highly inert, suggesting a 'partial double bond' character of the N–C(TFP) bond. As revealed by single-crystal X-ray diffraction analyses of 25 products, the molecular scaffold is robust exhibiting only small conformational changes. In the solid state, 2-chloro- and 2-bromo-substituted *N*-(tetrafluoropyridyl)sulfoximines link intermolecularly by halogen bonds of the type C–X···O=S providing 1D polymeric chains. In contrast, the 4-iodo-containing molecule forms a dimer bridged by C–I···π interactions. In $CDCl_3$ solutions, *S*-pyridyl *N*-(tetrafluoropyridyl)¬sulfoximines form halogen bonds to *N*-iodosuccinimide as revealed by ^{1}H NMR spectroscopy. The determined association constants K_a indicate that only $(CO)_2$N–I···N(*S*-pyridyl) complexes and no linkages between *N*-iodosuccinimide and the sulfoximine oxygen and TFP nitrogen are generated.

Experimental

Typical Procedure for the Synthesis of N-(2,3,5,6-tetrafluoro¬pyridyl)sulfoximines 3: A stainless-steel milling container (5 mL) equipped with one stainless-steel ball (7 mm in diameter) was charged with NH-sulfoximine 1 (50–100 mg), freshly ground KOH (3.00 equiv.), and pentafluoropyridine (2, 1.50 equiv.) in the given order. After the addition of 2, the jar was immediately closed. The reaction mixture was milled for 15 min at 25 Hz. After milling the reaction mixture was transferred to a flask by adding DCM (4 mL) to the jar, which was closed and shaken (3 cycles). Then, a small amount of silica was added to the flask, the volatiles were removed under reduced pressure, and product 3 was purified by column chromatography using a dry-loaded column.

Conflicts of interest

There are no conflicts to declare.

Acknowledgments

We are grateful to the Alexander von Humboldt Foundation and the Verband der Chemischen Industrie e.V. for support of K. R. (AvH research award) and C. S. (Kekulé scholarship), respectively. The research work was funded by the Academy of Finland (RP: grant no. 298817). The authors also acknowledge the University of Jyväskylä for providing SCXRD resources and Marcus Frings for helpful discussions.

Notes and references

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