Interaction of sulfinimines with boron Lewis acids †

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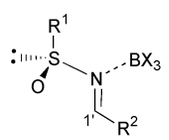
The interaction of sulfinimines with boron trifluoride etherate and boron trichloride has been investigated using ^{1}H, ^{13}C and ^{15}N NMR. The formation of 1 : 1 adducts was observed in $CDCl_3$ at −40 °C. The primary complexation of boron trihalides with sulfinimines occurred at the nitrogen atom. Shielding effects observed in ^{15}N NMR spectra suggest a medium strength interaction of the boron trihalides with the nitrogen atom. The complexation to the nitrogen atom was also manifested in chemical shifts and splittings of imino group resonances in ^{1}H and ^{13}C NMR.

Introduction

Optically active sulfinimines (*N*-alkyl or *N*-arylsulfinyl imines) have been found to be important starting materials for stereoselective synthesis of amines and their derivatives.[1] Apparently, the sulfinyl group not only activates the C=N bond but also directs nucleophiles in a highly stereoselective manner.[2] In addition, removal of the sulfinyl auxiliary from the product can be done under mild conditions and the chiral auxiliary may usually be recovered without loss of optical purity.

In the course of our work we have found that the addition of silyl ketene acetals to sulfinimines is strongly dependent upon the Lewis acid being used as a promoter.[3] The steric course of the reaction appears to be different from the well known addition of organometallic nucleophiles to sulfinimines. Other contributions have shown that reactions of sulfinimines with Grignard and organolithium compounds are influenced by the presence of Lewis acids[2,4–6] which is thought to be due to formation of adducts, either to the oxygen atom or to the nitrogen atom or both.



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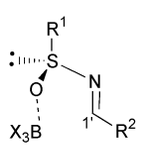

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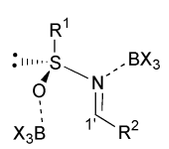

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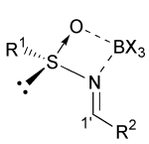

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These arbitrary models may usually be able to explain the observed stereoselectivity of the reactions. However, little is known about the real interaction between sulfinimines and Lewis acids in solution; the fundamental issue being that the site of interaction with the electrophilic reagents is difficult to characterise due to the ambident nature of this class of compounds and their chemical instability which makes them impossible to isolate. Theoretically, the Lewis acid may interact with the nitrogen, oxygen and/or sulfur atom, since all these basic centers are present in the sulfinimine molecule. For example, the protonation of sulfinamides has recently been a subject of controversy. From ^{14}N NMR chemical shifts and T_1 relaxation times it was concluded that aromatic and aliphatic sulfinamides are protonated at the oxygen atom.[7] However, preferential protonation at the nitrogen atom was suggested from IR, ^{13}C and ^{15}N NMR spectra.[8] Apparently, although sulfinamides and sulfinimines are related derivatives of sulfinic acids they differ substantially. The latter compounds possess an sp^2 hybridized nitrogen atom and will react with nucleophiles at the α-carbon atom.[1]

In the present work we have studied, with the aid of multinuclear magnetic resonance spectroscopy, the interaction of some aromatic and aliphatic sulfinimines with boron trihalides, compounds which appear to be efficient promoters of several studied reactions.[2–4,6,9]

Results and discussion

Two optically active sulfinimines, **1** and **2**, and a racemic, aromatic sulfinimine, **3**, were chosen as model compounds for this study. These compounds are known as useful starting materials in stereocontrolled syntheses. The sulfonylimine **4** represents a close analog of **3** and was chosen for comparison since the sulfonyl group is much less basic than the sulfinyl group.[10,11] All measurements were made in $CDCl_3$ or $CDCl_3$–CH_2Cl_2 mixtures. The latter solvent has been shown to give the best results in reactions with silyl nucleophiles.[3]

The ^{1}H NMR spectrum at room temperature of the mixture of sulfinimine **3** and $BF_3{\cdot}Et_2O$ in a molar ratio 1 : 0.8 showed only one set of broadened signals indicating fast exchange. The methylene group resonance of diethyl ether appeared as a broad singlet at 3.58 ppm. On cooling the solution to −20 °C, a sharpening of the resonances was observed and two sets of signals were observed, attributed to free and complexed sulfinimine. The chemical shifts did not change substantially within the range −20 to −60 °C. The use of excess BF_3 etherate showed the presence of a single adduct with the sulfinimines. The amount of free diethyl ether present in the solution suggested the adducts to have a 1 : 1 stoichiometry. The equilibrium constant for the reaction as shown by eqn. (1) as calculated from

† Electronic supplementary information (ESI) available: chemical shifts and assignments for compounds **1**–**4** at −40 °C in $CDCl_3$. See http://www.rsc.org/suppdata/p2/b1/b100465o/

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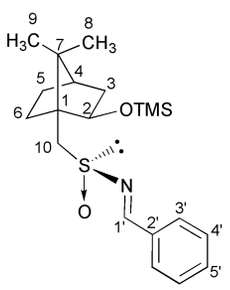
Table 1 ^{1}H NMR chemical shift differences (ppm) of compounds **1**–**4** and their boron trihalide complexes in $CDCl_3$ at −40 °C[a]

Position	Δδ(**1** + BF_3)	Δδ(**2** + BF_3)	Δδ(**3** + BF_3)	Δδ(**3** + BCl_3)	Δδ(**4** + BCl_3)
2	−0.01	−0.02	0.07	0.11	0.14
3	[b]	[b]	0.11	0.14	0.13
4	[b]	[b]	—	—	—
5	[b]	[b]	0.06	0.08	0.04
6	[b]	[b]	—	—	—
8	0.05	0.05	—	—	—
9	0.04	0.05	—	—	—
10	0.75, 0.18[c]	0.76, 0.20[c]	—	—	—
1′	0.09	0.29	0.14	0.23	0.19
2′	—	0.09	—	—	—
3′	0.03	[b]	0.07	0.14	0.21
4′	0.04	—	0.08	0.12	0.12
5′	0.12	—	0.14	0.20	0.21

[a] Shifts are referenced against residual $CHCl_3$ (7.26 ppm). Δδ is the chemical shift difference between complexed and uncomplexed compound. [b] Not assigned due to overlap. [c] Diastereotopic methylene protons.



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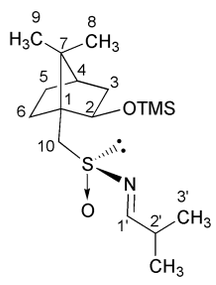

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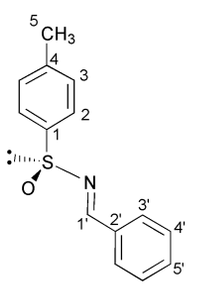

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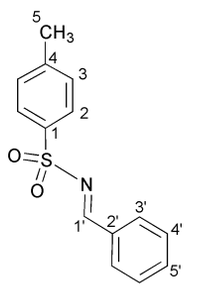

4

the chemical shifts of diethyl ether, ‡ observed at 24 °C was found to be 14. A value of 30 was obtained from the relative amounts of the species present in the equilibrium at −40 °C.

$$\mathbf{3} + BF_3{\cdot}Et_2O \rightleftharpoons \mathbf{3}{\cdot}BF_3 + Et_2O \qquad (1)$$

In the case of the 10-isobornylsulfinimines, **1** and **2**, the largest difference in the ^{1}H NMR chemical shifts was observed for the protons 10 and for imino proton 1′ (Table 1).

A similar shift to higher frequencies was also observed for the aromatic sulfinimine **3** with the largest shift at the 1′ position. The use of BCl_3, which is a stronger Lewis acid than BF_3,[12] resulted in an increase in these shift differences. The *N*-sulfonyl derivative, **4**, appeared to be less basic than the sulfinimines **1**–**3** since no changes in the spectra upon addition of $BF_3{\cdot}Et_2O$ could be detected (diethyl ether was not released from the BF_3 complex). However, with BCl_3 the expected adduct was formed and the effects in the ^{1}H NMR spectra were as for sulfinimine **3**.

Compounds **1**–**4** exist in $CDCl_3$ as single diastereoisomers and are believed to possess the *E* configuration; an X-ray study has revealed the *E* configuration in sulfinimine **3**.[13] Since the planar inversion barrier in sulfinimines is small[14] it is unlikely that they can exist in the more sterically demanding *Z* configuration. Although *E*–*Z* isomerization could not be detected during the described experiments with Lewis acids, it cannot be excluded. In the case of the BCl_3 complex with sulfonylimine **4** the ^{1}H NMR spectrum revealed broadening of the H-3′ signal due to hindered rotation around the C=N bond. The starting imines were recovered after quenching the reaction mixture at low temperature with an aqueous solution of $NaHCO_3$.

‡ The chemical shifts of diethyl ether in $CDCl_3$ at room temperature are as follows: complexed, δ 1.42, t, and 4.18, q; free δ 1.20, t, and 3.47, q.

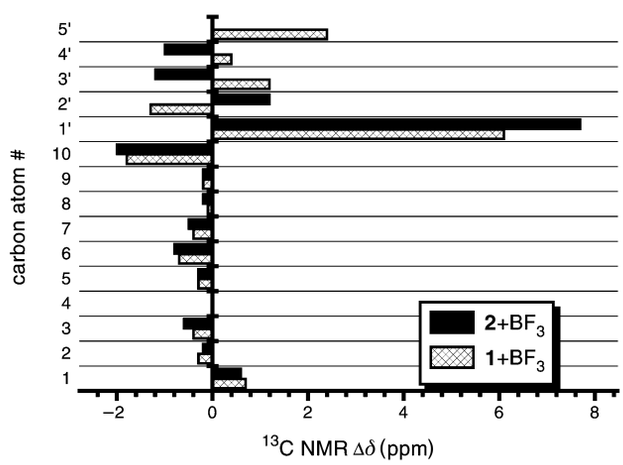

Fig. 1 ^{13}C NMR chemical shift differences of compounds **1**, **2** and their complexes with $BF_3{\cdot}Et_2O$ in $CDCl_3$ at −40 °C.

^{15}N NMR spectra of **1**–**3** with an excess of $BF_3{\cdot}Et_2O$ at −40 °C showed that the ^{15}N resonances are shifted by about 34 ppm to lower frequencies (Table 2). This difference did not change significantly at −60 °C (entries 8, 9, 10). The use of BCl_3, the stronger Lewis acid, increased the shifts by 50 ppm in the case of sulfinimine **3**. These shielding effects indicate a medium strength N···B interaction since protonation of imines usually results in an upfield shift of *ca.* 100 ppm,[15] compared with a change on hydrogen bonding of only *ca.* 20 ppm.[16] However, BH_3 adducts with imines have resonances shifted to lower frequencies by 82 ppm.[17] A similar Δδ value (86 ppm) was observed in the ^{14}N NMR spectra of boron tribromide complexes with pyridine.[18] The ^{15}N NMR shielding effect of 64.5 ppm observed for the nitrogen atom in sulfonylimine **4** was higher than in the related sulfinimine **3** (49.7 ppm). This is a rather surprising result since Δδ values in ^{1}H and ^{13}C NMR (*vide infra*) are equal or much higher for sulfinimine **3** than they are for sulfonylimine **4**.

The ^{13}C NMR spectra showed the largest deshielding for the imino carbon atom C-1′ (Fig. 1 and 2) and a large shielding increase of the carbon atom adjacent to the sulfur atom (C-10 for **1**, **2** and C-1 for **3**, **4**) upon addition of boron trihalides. The

Table 2 ^{15}N NMR chemical shifts of sulfinimines **1**–**3**, sulfonylimine **4** and their complexes with boron trihalides in $CDCl_3$[a]

Entry	Compound	Temp./ °C	δ (ppm)	$\Delta\delta$ (ppm)
1	**1**	−40	−56.5	—
2	**1** + $BF_3{\cdot}Et_2O$	−40	−93.2	−36.7
3	**2**	−40	−57.2	—
4	**2** + $BF_3{\cdot}Et_2O$	−40	−85.5	−28.3
5	**3**	−40	−57.3[b]	—
6	**3** + $BF_3{\cdot}Et_2O$	−40	−95.0	−37.7
7	**3** + BCl_3	−40	−107.0	−49.7
8	**3** + $BF_3{\cdot}Et_2O$[c]	−20	−94.3	−37.0
9	**3** + $BF_3{\cdot}Et_2O$[c]	−40	−95.3	−38.0
10	**3** + $BF_3{\cdot}Et_2O$[c]	−60	−96.0	−38.7
11	**4**	−40	−65.3	—
12	**4** + BCl_3[c]	−20	−129.8	−64.5

[a] CH_3NO_2 was used as spectral reference. $\Delta\delta$ is the chemical shift difference between complexed and uncomplexed compound. Accuracy of measurements was ± 0.5 ppm. [b] $^2J_{NH}$ = 5.9 Hz. [c] $CDCl_3$ + CD_2Cl_2, 1 : 1.

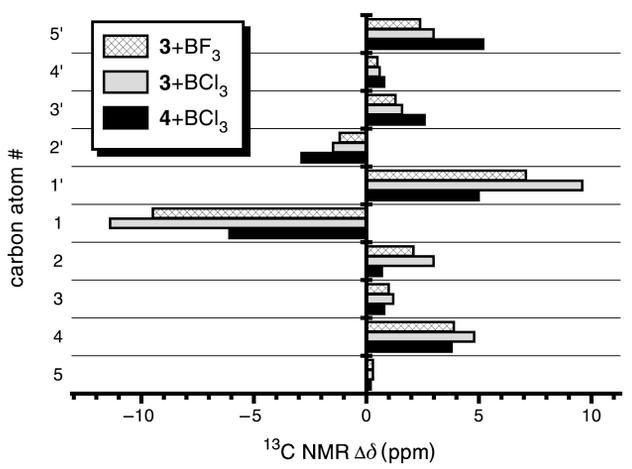

Fig. 2 ^{13}C NMR chemical shift differences of compounds **3**, **4** and their complexes with boron trihalides in $CDCl_3$ at −40 °C.

effects are as observed for adducts of aliphatic and aromatic ketimines with BH_3.[17] In these complexes the imino carbon resonance was shifted to higher frequency by *ca.* 11 ppm and the signal due to the carbon in the β-position in the *N*-alkyl chain of the imine was shifted to a lower frequency by *ca.* 3 ppm.[17] However, the larger shielding effects on carbon C-1 in imine **3** than in imine **4** may suggest interaction with the sulfinyl oxygen atom since the basicity of the sulfonyl group is much lower.[10]§ Alternatively, this effect may be attributed to improved transmission of electronic effects (caused by nitrogen atom complexation) through the sulfur atom in the SO moiety. Interaction of methyl phenyl sulfoxide with BF_3 etherate in $CDCl_3$ at 24 °C resulted in an upfield shift for the *ipso* carbon atom by 11.9 ppm and the methyl resonance by 5.8 ppm. This is slightly more than observed for the carbon atom adjacent to the sulfur atom in sulfinimine **3** as well as in **1** and **2**. Interaction at the sulfur atom, which is the third basic center in sulfinimines, seems to be most unlikely as viewed by the ^{1}H and ^{13}C NMR chemical shifts of the BCl_3 complexes with **3** and **4**. Similar conclusions have been made for sulfinamides.[7,8] Chemical shift changes of C-2′ showed the same pattern as observed for simple *N*-protonated imines,[19] *i.e.* an upfield shift for the *ipso* carbon atom in aromatic imines and a downfield shift of C-α resonances in imines being substituted with an aliphatic group. For sulfinimines **1** and **3** we were able to observe scalar coupling to fluorine in the ^{13}C NMR spectra. The signal due to the imino carbon appeared as a quartet with coupling constants of 1.4 and 1.2 Hz, respectively. In the case of compound **2** this resonance was broadened (half linewidth 3.3 Hz). It is unlikely that this coupling originates from an *O*-complexed compound ($^5J_{CF}$) and therefore strongly supports the presence of a type **A** complex ($^3J_{CF}$). In comparison, the $^3J_{CF}$ coupling constant observed on the C-α resonance in $BF_3{\cdot}Et_2O$ was 2.1 Hz. The spectra of sulfinimine **3**, recorded both with a substoichiometric amount and with an excess of BF_3 etherate, showed the same chemical shifts for the complexed species. This is strong evidence for primary complexation at the nitrogen atom.

Boron Lewis acids have commonly been regarded as nonchelating. However, recently it was shown that α- and β-methoxyketones can form five- or six-membered ring complexes with tris(pentafluorophenyl)borane, where the boron atom is hypervalent.[20] Pentacoordinate organoboron complexes of β-methoxyketones showed very large upfield shifts in ^{11}B NMR spectra compared to tetracoordinated complexes of simple ketones.[21] The simultaneous complexation of the oxygen and the nitrogen atoms in sulfinimines by boron trihalides (structure **D**) is very unlikely because such a four-membered ring would be sterically very unfavourable. Indeed, the ^{11}B NMR resonances of the sulfinimine **3** complex with BF_3 and BCl_3 at −40 °C were shifted to lower frequency by 0.2 and 37.7 ppm respectively. Similarly, the ^{11}B NMR chemical shift of the BCl_3 complex with sulfonylimine **4** was shifted by 39 ppm. These values are typical for a four-coordinate boron atom complexed to an sp^2 type nitrogen atom. For example, pyridine complexes with BF_3 and BCl_3 are shifted by 0.3[22] and 37.8[23] ppm respectively.

^{17}O NMR spectroscopy has been shown to be a sensitive tool for investigation of interactions with the oxygen atom.[24] However, low temperature measurements are quite difficult to perform due to line broadening of ^{17}O resonances in the more viscous solvents. The ^{17}O NMR chemical shift of sulfinimine **3** at 30 °C was 70 ppm (CH_2Cl_2 + $CDCl_3$, 1 : 1, relative to H_2O) with a half linewidth of 220 Hz. On lowering the temperature to −20 °C, an increase in $\nu_{\frac{1}{2}}$ to 740 Hz (δ 69 ppm) was observed. Upon addition of $BF_3{\cdot}Et_2O$ this resonance line could not be detected. Signals corresponding to diethyl ether appeared at 17 (free) and 26 ppm (complexed to BF_3).

The present results are in agreement with the chemical properties of sulfinimine–Lewis acid mixtures. However, the reactivity of such systems is lower than expected. For example, sulfinimines react with silyl ketene acetals but not with the less reactive silyl enol ethers[3] indicating that activation of the C=N bond is weak. The influence of Lewis acids on the observed stereoselectivity suggests that complexation of the oxygen atom cannot be negligible despite the lack of unquestionable spectral evidence. In view of the results discussed above, strongly suggesting that structures **B** (alternative complexation on oxygen) and **D** (chelation of N and O) are unlikely, the altered stereoselectivity using boron halide complexes suggests that complexation of a second molecule on oxygen (structure **C**) may be occurring.

Conclusions

The above findings strongly indicate that the primary complexation of boron trihalides with sulfinimines takes place at the nitrogen atom (structure **A**). However, the ^{15}N NMR shielding effects which are significant but not large suggest that this interaction is fairly weak. The possibility of a simultaneous complexation at the oxygen atom by an excess of a Lewis acid (structure **C**) can not definitively be ruled out (and may be responsible for the stereoselectivity observed); but if so, the equilibrium must be shifted toward complex **A**. An equilibrium between *N*- and *O*-complexed forms (*i.e.* **A** ⇌ **B**) is unlikely at low temperatures. The formation of four-membered chelates of type **D** can also be excluded in view of the ^{11}B NMR spectra.

§ For comparison, enthalpies (kJ mol^{-1}) of complex formation with BF_3 are: tetramethylenesulfone 51.3, Et_2O 78.8, DMSO 105.3, pyridine 128.1. Ref. 11.

Experimental

Compounds **1** and **2**,[3] **3**[13] and **4**[25] were prepared by known methods. Boron trichloride was used as a 1 M solution in CH_2Cl_2 (Aldrich). Boron trifluoride etherate was distilled from CaH_2 prior to use. $CDCl_3$ was dried with $MgSO_4$ and molecular sieves. All samples were prepared in an argon atmosphere. The Lewis acid was added to the sulfinimines at room temperature and the samples were immediately inserted into the NMR probe cooled to −40 °C. The concentration of the solutions was usually 0.15 M. ^1H and ^{13}C NMR experiments were performed on a Varian INOVA 500 spectrometer. The 2D ^1H-^{15}N gradient selective HMQC and HSQC experiments optimized on a 6 Hz coupling constant were conducted on a Bruker AVANCE 500 spectrometer.

Acknowledgements

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