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Aminolysis of sulfinamoyl-esters, -sulfonamides and -sulfones. Thiooxamate and thiourea formation via a sulfine intermediate. Thiophilic or carbophilic reaction ?

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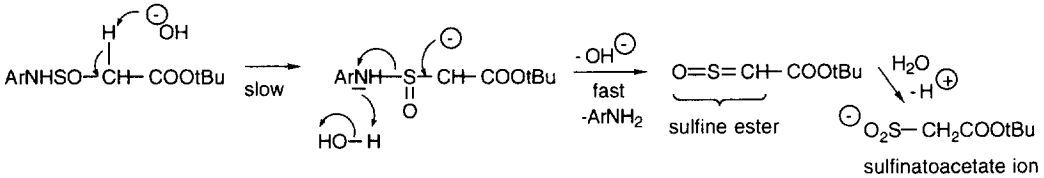
Abstract: The aminolysis process of sulfinamoyl derivatives was investigated with sulfinamoyl esters. An intermediate sulfine was unambiguously evidenced by formation of a Diels-Alder type adduct. The aminolysis leads to final thiooxamate products. A carbophilic addition was suggested for the reaction with secondary amines. With sulfinamoyl, -sulfones and -sulfonamides, a thiourea is formed resulting from a double aminolysis. Copyright © 1996 Elsevier Science Ltd

Cinnamoyl alcohol dehydrogenase, a zinc-containing metalloenzyme (CAD2, E.C.1.1.1.1.195),[1] is one of the enzymes controlling the first committed steps of lignification and transforms cinnamaldehydes to the corresponding alcohols using NADPH as cofactor. In the course of our studies towards evaluation of inhibitors of CAD we have synthesized a series of sulfinamoylacetates.[2] These compounds bearing a sulfinamide functionality and an α-activated methylenic group are specific *in vitro* and *in vivo* inhibitors of CAD.[3] Their complexing properties have been determined[4] and their transformation through hydrolysis[5] and aminolysis[6] has been studied. These two reactions can best describe the activity of the sulfinamoyl esters at the active site of the CAD, where a reactive water molecule is bound to the metal and cysteine, histidine amino acids bind the active zinc atom[1] and may participate in the enzymatic process. Our studies have shown in both transformations that a sulfine intermediate may be formed through the reaction pathway, leading to sulfinic acid (hydrolysis) (scheme 1) or thiooxamate (aminolysis). The sulfine intermediate might be responsible for suicide inactivation of CAD observed in some cases with sulfinamoyl esters.



Scheme 1

Activated methylenic group α to the sulfinamide moiety is a necessary condition for the reactions to occur. In order to evaluate the reactivity of compounds ($ArNHSOCH_2X$) including such groups, we report here the synthesis and aminolysis reaction of sulfinamoyl esters ($X = CO_2R$), sulfinamoyl sulfones ($X = SO_2R$) and sulfinamoyl sulfonamides ($X = SO_2N(R')Ph$), and demonstrate that a sulfine is an intermediate electrophile of the reaction. A mechanistic pathway exploring either a carbophilic or a thiophilic attack of the sulfine will be proposed and discussed.

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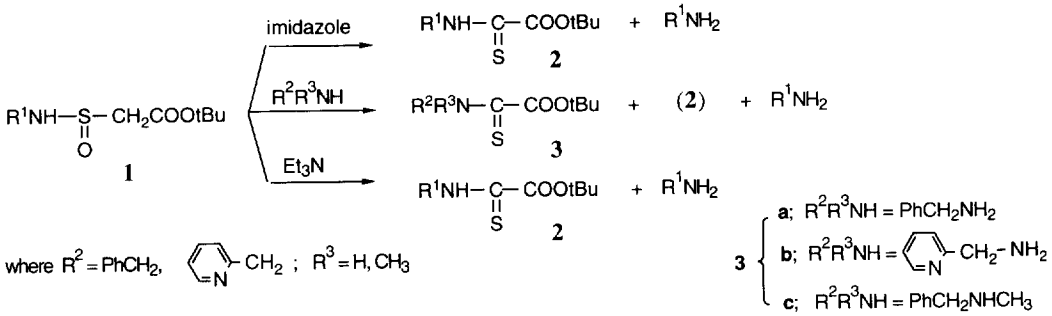
RESULTS

Sulfinamoyl esters. Our first results on aminolysis of sulfinamoyl esters[6] led to different thiooxamates **2, 3** depending on the involved amine (scheme 2, Table 1).



Scheme 2

In all cases the same protocol was used: t-butyl sulfinamoylacetates react at room temperature in acetonitrile or diethyl ether solutions with a threefold excess of amine. The reaction is followed by TLC until disappearance of the substrate. The reaction mixture is then dried over $MgSO_4$ and chromatographied on silica gel (petroleum ether : ether 80:20) to give thiooxamates in fair to good yields (table 1). They are characterized by analytical and spectroscopic methods.[6]

Table 1. Reaction of t-butyl sulfinamoyl acetates $R^1NHSOCH_2COOtBu$ with various amines

Entry	Substrate	R^1	Amine	Solvent	Reaction time (h)	Product	Yield (%)	R^1NH_2 recovered (%)
1	**1a**	C_6H_5	imidazole	CH_3CN	72	**2a**	86	5
2	**1b**	3-ClC_6H_4	imidazole	CH_3CN	36	**2b**	65	10
3	**1c**	4-ClC_6H_4	imidazole	CH_3CN	36	**2c**	69	5
4	**1d**	4-$OMeC_6H_4$	imidazole	CH_3CN	36	**2d**	73	5
5	**1e**	C_6H_{11}	imidazole	CH_3CN	36	**2e**	60	10
6	**1a**	C_6H_5	$PhCH_2NH_2$	CH_3CN	36	**3a**	45	100
		C_6H_5	$PhCH_2NH_2$	Et_2O	72	**3a**	63	100
7	**1f**	4-$NO_2C_6H_4$	$PhCH_2NH_2$	Et_2O	48	**3a**	41	100
8	**1b**	3-ClC_6H_4	$PhCH_2NH_2$	Et_2O	72	**3a**	43	100
9	**1a**	C_6H_5		CH_3CN	36	**3b** + (**2a**)	35(9)	56
10	**1a**	C_6H_5	$PhCH_2NHCH_3$	CH_3CN	16	**3c**	57	60
11	**1a**	C_6H_5	Et_3N	CH_3CN	36	**2a**	25	45
12	**1g**	*o*-HOC_6H_5	imidazole	CH_3CN	36	**2'g**	32	-

With a weak secondary amine such as imidazole (pKA = 7.2) the product **2** results from a rearrangement of the starting sulfinamoyl acetate with loss of a water molecule: the overall effect of the amine is a general catalysis (Table 1, entries 1-5).

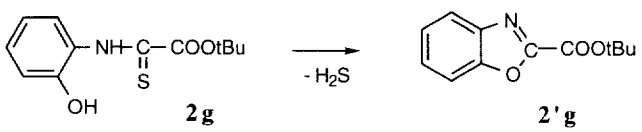
With a strong primary amine such as benzylamine (pKA = 9.60) the nature of thiooxamate **3a** reveals an amine group substitution indicating the participation of the amine as a nucleophile. This substitution is also illustrated by the quantitative recovery of the arylamine liberated from the sulfinamoyl acetate (Table 1, entries 6-8) while it is very poor when the amine is imidazole. The field desorption mass spectrum of compound **3a** presents along with the characteristic tropylium ion (m/z = 91) two peaks, one at m/z = 251 corresponding to the thiooxamate **3a**, the other at m/z = 502 related to its dimeric form.[6] However osmometric measurements agree only with the monomer (M.W. = 235).

When a primary amine of intermediate strength as 2-(aminomethyl)pyridine (pKA = 8.65) is used, a mixture of both thiooxamates **2** and **3** is obtained and aniline is recovered at 56% yield (Table 1, entry 9).

With the strong secondary amine, N-methylbenzylamine (pKA = 9.82), sulfinamoylacetate **1a** leads to the thiooxamate **3c** with a fair yield (57%) and aniline is recovered (60% yield) (Table 1, entry 10). The nmr spectrum of **3c** indicates a 60/40 ratio of two isomers in relation with the restricted rotation around the C-N bond of the thioamide moiety. High values for the rotational barrier energy have been reported [7,8] for such a process. Coalescence temperature of their ^1H NMR signals in o-dichlorobenzene could not be fully observed at the 150 °C maximum temperature; it is in agreement with a barrier energy larger than 22 kcal mol^{-1}.

The reaction with a strong tertiary amine triethylamine (pKA = 11.0) gives the thiooxamate **2** in a modest yield while the amount of aniline is greatly increased (Table 1, entry 11).

Finally, in the case of **1g** (entry 12), with the same protocol, the expected thiooxamate was not obtained: the t-butyl benzoxazole carboxylate **2'g** was isolated and characterized through analytical and spectroscopic methods. The product could result from intermediate thiooxamate formation, followed by a cyclization reaction involving the phenol group with elimination of H_2S (Scheme 3).



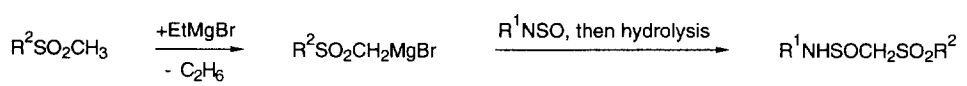
2g **2'g**

Scheme 3

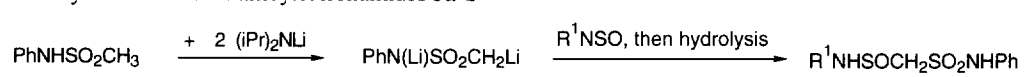
Sulfonamoyl sulfones 4 and sulfonamides 5. Compounds $R^1NHSOCH_2SO_2R^2$ (Table 2) were synthesized by condensation of sulfinylamines R^1NSO with the mono- (scheme 4, method 1) or di- (method 2) organometallic derivative of a methyl sulfone or a methanesulfonamide.

The behaviour of these compounds towards aminolysis might differ from that of sulfinamoyl esters **1** due to the presence of a more acidic α-sulfonyl methylenic group.

Method 1: Synthesis of sulfinamoyl sulfones **4a-f** and sulfonamide **5c**



Method 2 Synthesis of sulfinamoylsulfonamides **5a-b**



Scheme 4

Table 2. Preparation of sulfinamoyl-sulfones and -sulfonamides R^1-NH-SO-CH_2-SO_2-R^2

Product	R^1	R^2	Preparation method	Yield (%)	m.p. (°C)
4a	Ph	Ph	1	73	149
4b	3-ClPh	Ph	1	54	161
4c	4-ClPh	Ph	1	58	143
4d	2-OHPh	Ph	1	24	oil
4e	4-NO_2Ph	Ph	1	50	205
4f	4F_3C-Ph	Ph	1	62	213
5a	Ph	-NHPh	2	43	157
5b	3-ClPh	-NHPh	2	41	140
5c	Ph	-N(CH_3)-Ph	1	29	108

Spectroscopic data are listed in the experimental section.

The aminolysis of **4a**, **5a** and **5c** was performed in order to obtain the analogous thiooxamate compounds $R^1NHC(S)$-SO_2R^2 i.e. thioamide-sulfone (R^2 = Ph) or -sulfonamides (R^2 = PhNH, $PhNCH_3$), but when we used the protocol described for thiooxamates, the expected compounds were not isolated. Results are given in Table 3.

Table 3. Aminolysis of sulfinamoylsulfone **4a** and sulfonamides **5a**, **5c** in CH_3CN at 25 °C

Substrate	Amine	Reaction time (h)	Products	Yield (%)
4a	imidazole	0.2	PhNHC(S)NHPh **8a**	50
5a	imidazole	2	PhNHC(S)NHPh	50
	$BnNH_2$	2	BnNHC(S)NHBn **8b**	70
			CH_3SO_2NHPh	traces
5c	$BnNH_2$	2	BnNHC(S)NHBn	30
			CH_3SO_2NMePh	40
			PhNHMe	67
			$PhNH_2$	27

With imidazole at 25 °C, **4a** and **5a** led to the same N,N'-diphenylthiourea as main product. No reaction occurred with **5a** in imidazole at 0 °C for 2 h.

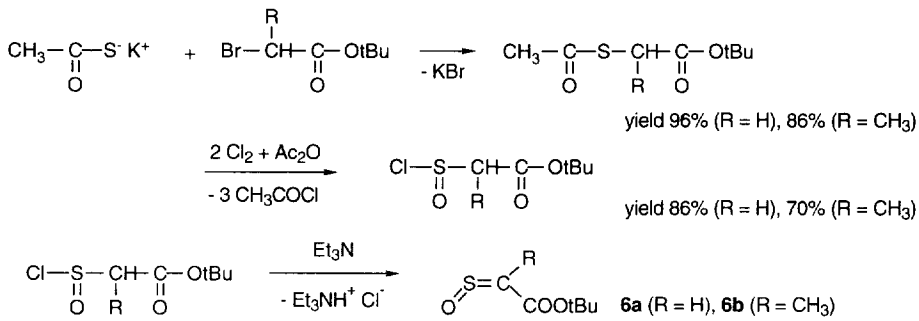
The addition of a strong primary amine, benzylamine, to **5a** gave the thiourea with amine transfer in a 70% yield, and traces of N-phenylmethylsulfonamide. When **5c** was treated with benzylamine four compounds were isolated after purification on silicagel (hexane/ether, gradient 90/10 to 50/50): the thiourea with amine transfer, the methanesulfonamide, and two amines : aniline and N-methylaniline.

Synthesis of two α-functionalized sulfines. Evidence for a sulfine intermediate. The t-butyl thioxoacetate S-oxide **6a** O=S=CH-CO_2tBu which was postulated as an intermediate electrophile at the active site of CAD enzyme during hydrolysis[5] or aminolysis unmasking process[6] of sulfinamoyl esters could not be isolated due to the high reactivity of the sulfine moiety. However such sulfines have been trapped by dienophiles giving Diels-Alder adducts.[9]

Synthesis and characterization of 6a, b. In a first attempt, we decided to synthesize the thioketone S-oxide **6b** where the replacement of an hydrogen atom by a methyl group on the thiocarbonyl carbon might improve the stability.

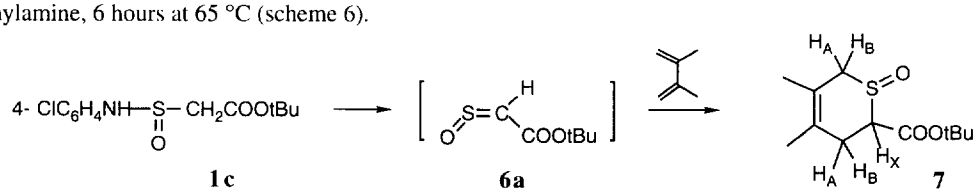
It was obtained in a three step sequence involving a sulfinyl chloride intermediate,[2b] which was dehydrochlorinated with Et_3N (scheme 5). After HPLC purification this sulfine **6b** was obtained in a 62% yield. It was identified by ^{13}C nmr spectroscopy (δ = 184.4 ppm for the C=S group), by infrared spectroscopy ($\nu S{=}O$ = 1105 cm^{-1}) and by mass spectrometry (DCI/NH_3, 194 ($M+NH_4^+$)). Its adduct with 2,3-dimethylbutadiene could not be isolated.

Using the same sequence the sulfine **6a** was obtained and kept in ethyl ether solution to avoid a possible decomposition. Immediate mass spectrometry (DCI/NH_3) analysis indicated the presence of a dimeric form with peaks at 342 ($2M+NH_4^+$) and 326 ($2M+2H^+$). Such a dimerisation has been also suggested for the lachrymogenic principle of onion.[10]



Scheme 5

Evidence of the sulfine intermediate. A Diels-Alder reaction, was carried out with sulfinamoyl ester **1c** and 2,3-dimethylbuta-1,3-diene using the conditions described by Kirby[9]: solvent benzene, catalytic quantity of triethylamine, 6 hours at 65 °C (scheme 6).



Scheme 6

The cyclo-adduct **7** was isolated by chromatography (silica column, ether, yield 40%). Significantly ^1H nmr spectrum showed signals consistent with an AB system (δ_A = 3.03 ppm, δ_B = 3.23 ppm, J_{AB} = 16.6 Hz) and an ABX system (δ_A = 2.45 ppm, δ_B = 2.67 ppm, δ_X = 3.71 ppm, J_{AB} = 18 Hz, J_{AX} = 7 Hz, J_{BX} = 4.5 Hz). The singlet at 1.42 ppm is assigned to the tert-butyl group and the signal at 1.67 ppm to the protons of the two methyl groups.

The H_X signal of compound **7** has the same chemical shift (δ = 3.71 ppm) than the analogous proton of the cycloadduct prepared by Kirby[9] which only differs from **7** by an ethyl ester function. ^{13}C NMR and IR spectra are also consistent with the postulated structure **7**.

DISCUSSION

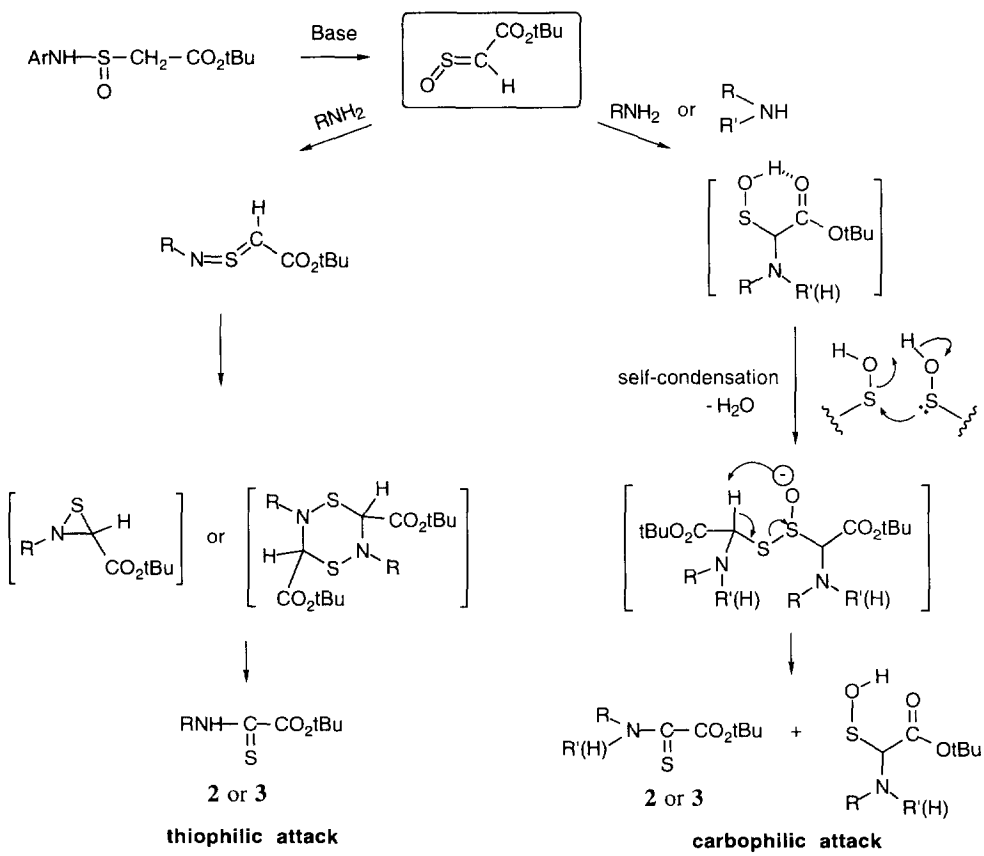
A sulfine intermediate has been postulated from kinetic data[5] for the alkaline hydrolysis of sulfinamoyl esters (scheme 1), and the trapping experiment giving a Diels-Alder adduct from the sulfinamoyl esters demonstrates that it is actually involved.

For the aminolysis of sulfinamoyl esters, sulfones or sulfonamides an analogous reactivity associated with the acidity of the methylenic group was anticipated leading to the corresponding sulfine.

The second step of the pathway leading to thiooxamates or thioureas is more puzzling.

The reaction of sulfines with amines is little known[11] and presents the case of carbon *versus* sulfur addition of nucleophiles to sulfines. In a recent paper Metzner *et al.*[12] gave evidence for a carbophilic addition of amines on dithioester sulfines instead of thiophilic addition.

Sulfinamoyl esters. In a previous paper[6] we have proposed for sulfinamoyl esters a thiophilic addition with a thione S-imide intermediate. Both carbophilic and thiophilic reactions are represented in scheme 7.



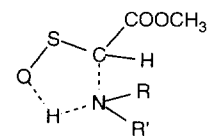
Scheme 7

The sulfine reacts either with the leaving amine or with the added amine or both depending on their nucleophilicity.

A thiophilic attack gives a thione S-imide which dimerises to a cyclic sulfenamide which after proton transfer and N-S bond scission rearranges yielding the corresponding thiooxamates. Thione S-imides are known as reaction intermediates[13] or stable compounds.[14] Nevertheless in all the quoted cases, a hydrogen atom at the sp^2 carbon or the nitrogen atom of the thione S-imide function is lacking. They have been also reported as precursors of cyclic three membered sulfenamides which undergo desulfurization to yield imines.[13] This thiophilic mechanism has been preferred versus the carbophilic pathway which has been postulated[11b] when the sulfine bears a potential leaving group such as Cl^-, PhS^- which is the case with Metzner's sulfines.[12] In our case, the ester group is not a good leaving group; moreover the sulfur atom bears a high positive charge.

This was shown by *ab initio* calculations performed at the Hartree-Fock level on the sulfine model $O{=}S{=}CH\text{-}COOCH_3$. Four isomers corresponding to E/Z isomerizations by rotation either around the C-S bond or around the C-C bond have been fully optimized. A vibrational analysis reveals a Cs symmetry, supporting a planar geometry for the sulfine fragment, for all cases studied. Mulliken population analyses indicate charge densities ranging from -0.53 to -0.56 for oxygen, from +0.61 to +0.67 for sulfur, and from -0.29 to -0.33 for carbon. These results are in good agreement with those previously obtained by Block et al[15] on the S-oxide of thioformaldehyde $O{=}S{=}CH_2$ (-0.58 for oxygen, +0.51 for sulfur and -0.37 for carbon). Therefore the sulfur atom appears to be a strong electrophilic center which may interact with the nitrogen lone pair of a primary or secondary amine according to a thiophilic attack.

However, a thiophilic mechanism cannot be involved in the reaction with a secondary amine giving amine transfer and so, we reexamined the carbophilic attack. Such a mechanism can be considered if we suppose a transient association of the amine with the sulfine through the formation of an hydrogen bond with the highly negatively charged oxygen atom as depicted beside, then the breaking of the N-H bond and the formation of a C-N bond involving the oxygen-protonated form of the sulfine.[16] A Mulliken population analysis performed on $[HO\text{-}S\text{-}CH\text{-}COOCH_3]^+$ indicates a change of sign of the CH group charge with respect to the value obtained in the sulfine (+0.21 versus -0.11). Therefore the CH group can react with the remaining fragment of the amine to form the C-N bond. A concerted mechanism through a five-membered transition state may be also considered.



The intermediate sulfenic acid (Scheme 7) can be stabilized by internal H-bond as postulated by Block[17] for an analogous β-sulfoxide compound. Then, a self-condensation process should lead to the thiosulfinate ester following a described process.[18] Finally, the conversion to a thioamide should be facilitated by the abstraction of the acidic hydrogen atom activated by the ester function.[19]

Of course, the initial step of the carbophilic attack could be the same in the case of a primary amine, and a more precise study of the whole mechanism will have to be undertaken to fully inderstand why a carbophilic reaction seems to be preferred.

Sulfinamoyl-sulfones and -sulfonamides. The obtention of thiourea (Table 3) from sulfinamoyl-sulfones or -sulfonamides can be explained by the intermediate formation of a thioamide sulfone or sulfonamide $PhNHC(S)E$, with E = SO_2Ph or SO_2NRPh following one of the mechanisms previously described for sulfinamoyl esters.

The subsequent nucleophilic attack of the added benzylamine or of the aniline liberated by scission of the N-S sulfinamide bond through the basic catalysis by imidazole leads to the thiourea with elimination of the good leaving group E. At low temperature (0 °C), no reaction was observed in acetonitrile.

When sulfinamoyl sulfonamides are reacting with benzylamine, other fragmentations intervene essentially for compound **5c**. These scissions involve in addition the S-C and S-N sulfonamide bonds as summarized in Table 4 from results listed in Table 3.

Table 4. Aminolysis mechanism of the sulfinamoyl sulfonamide **5c** with benzylamine in CH_3CN at 25 °C

	Type of primary scission	Products	Percentage
1	PhNH–{–S(O)CH_2SO_2NMePh	BnNHC(S)NHBn PhNHMe $PhNH_2$	30
2	PhNHS(O)–{– CH_2SO_2NMePh	CH_3SO_2NMePh	40
3	PhNHS(O)CH_2SO_2–{– NMePh	PhNHMe	30

The type 1 fragmentation is responsible of the thiourea formation while the obtention of methylphenylsulfonamide is only explained by a type 2 mechanism. The excess of N-methylaniline requires the involvement of type 3 scission.

The two later types should also give at the same time sulfinic or/and aminosulfinic acids which were not isolated. They could be retained on the column during chromatography. They do not appear in tables 3 and 4.

EXPERIMENTAL SECTION

Melting points were determined on a Kofler apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 883 spectrophotometer in potassium bromide discs. ^1H magnetic resonance spectra (80 MHz) and ^{13}C magnetic resonance spectra (50.3 or 62.9 MHz) were recorded on Bruker AC-80 and AC-200 spectrometers. Data are reported in the following order: chemical shift, spin multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet), integration and assignment. Mass spectra (MS) were performed with a NERMAG R10-10C spectrometer using the electron impact (EI) or desorption chemical ionization (DCI/NH_3) techniques. Elemental analyses were carried out by the "Service Commun de Microanalyse élémentaire UPS-INP" in Toulouse. Analysis and preparative HPLC were performed on Kratos (UV detector 759) and Waters (UV diode-array detector 950) systems.

General procedure for the preparation of thiooxamates 2 and 3 and benzoxazole 2'g from sulfinamoyl esters

The t-butyl N-aryl(or alkyl)-sulfinamoyl acetates precursors **1a-g** were prepared according to the previously described methods.[2a, b] The bases imidazole, triethylamine, benzylamine, N-methyl benzylamine and 2-pyridylmethylamine are commercial. Typically, an excess of imidazole (0.475 g, 5 mmol) in acetonitrile (5 mL) was added dropwise under dry nitrogen, at room temperature to a solution of t-butyl N-phenylsulfinamoylacetate **1a** Ph-NH-SO-CH_2-COOtBu (0.400 g, 1.6 mmol) in acetonitrile (15 mL). Mixture was stirred for 72 h, till total disappearance of substrate, controlled by TLC, then dried on $MgSO_4$ and solvent evaporated in vacuum. HPLC on silica (petroleum ether/ether 80/20) afforded purified **2a** as a dark yellow oil (0.326 g, 86%). Yields of thiooxamates and benzoxazole are given in Table 1 and spectroscopic data below. **2a**

Orange oil. IR ($CHCl_3$) ν cm^{-1}: 3310 (NH); 1705 (C=O); 1595 and 1530-1490 (CC arom.); 1390 (C=S); 1305; 1155 (COC). ^1H NMR ($CDCl_3$) δ ppm: 1.61 (s, 9H, 3xCH_3); 7.10-8.10 (m, 5H, Ph); 10.60 (s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ ppm: 27.71 (CH_3); 71.85 (CMe_3); 121.99, 127.23, 129.11, 137.91 (C arom.); 158.5 (C=O); 180.99 (C=S). MS (EI) m/z: 237 ($M^{+\cdot}$); 181; 136; 101. Anal. calcd for $C_{12}H_{15}NO_2S$: C, 60.73; H 6.37; N, 5.90. Found: C, 60.95; H, 6.55; N, 5.65.

2b Orange oil. IR ($CHCl_3$) ν cm^{-1}: 3311 (NH); 1706 (C=O); 1589, 1479 (CC arom.); 1375 (C=S); 1305, 1155 (COC). ^1H NMR ($CDCl_3$) δ ppm: 1.60 (s, 9H, 3xCH_3)); 7.20-8.14 (m, 4H, Ph); 10.54 (s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ ppm: 27.67 (CH_3); 65.58 ($\underline{C}Me_3$); 120.14; 121.85; 127.19; 130.10; 134.69; 138.96 (C arom.); 158.24 (C=O); 181.51 (C=S). MS (EI) m/z: 273; 271 ($M^{+\cdot}$); 113; 111. Anal. calcd for $C_{12}H_{14}NO_2SCl$: C, 53.04; H 5.19; N, 5.15. Found: C, 52.99; H, 5.15; N, 5.41.

2c Orange solid, m.p. 105 °C. IR ($CHCl_3$) ν cm^{-1}: 3313 (NH); 1707 (C=O); 1302; 1155 (COC). ^1H NMR ($CDCl_3$) δ ppm: 1.61 (s, 9H, 3xCH_3); 7.25-7.96 (dd, 4H, Ph); 10.56 (s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ ppm: 27.69 (CH_3); 85.56 ($\underline{C}Me_3$); 123.18; 129.22; 132.15; 136.42 (C arom.); 158.35 (C=O); 181.12 (C=S). MS (DCI/NH_3) m/z: 272 ($M^{+\cdot}$); 273, 274, 275, 289 ($M+NH_4^+$); 290, 291, 292.

2d Orange oil. IR ($CHCl_3$) ν cm^{-1}: 3320 (NH); 1705 (C=O); 1610; 1515 (CC arom.); 1463; 1395 (C=S); 1305; 1157 (COC). ^1H NMR ($CDCl_3$) δ ppm: 1.60 (s, 9H, 3xCH_3)); 3.81 (s, 3H, CH_3); 6.90-7.00 and 7.80-7.90 (m, 4H, Ph); 10.56 (s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ ppm: 27.69 ($C\underline{Me}_3$); 55.62 (O-$\underline{C}H_3$); 85.15 ($\underline{C}Me_3$); 114.09; 123.77; 131.06; 158.24 (C arom.); 158.33 (C=O); 180.30 (C=S). MS (EI) m/z: 267 ($M^{+\cdot}$); 211; 166; 108; 92. Anal. calcd for $C_{13}H_{17}NO_3S$: C, 58.40; H 6.41; N, 5.24. Found: C, 58.71; H, 6.31; N, 5.49.

2e Orange oil. IR ($CHCl_3$) ν cm^{-1}: 3338 (NH); 1706 (C=O); 1510; 1453; 1397 (C=S); 1296; 1156 (COC). ^1H NMR ($CDCl_3$) δ ppm: 1.20-2.10 (m, 19H, 3xCH_3, C_6H_{11}); 4.14-4.35 (m, 1H, C_6H_{11}); 8.80 (s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ ppm: 24.53; 25.42; 30.69; 54.11 ($\underline{C}_6H_{11}$); 27.66 (CH_3); 64.72 ($\underline{C}Me_3$); 158.54 (C=O); 183.04 (C=S). MS (EI) m/z: 243 ($M^{+\cdot}$); 188; 187; 169; 112. Anal. calcd for $C_{12}H_{21}NO_2S$: C, 59.22; H 8.70; N, 5.76. Found: C, 58.98; H, 8.68; N, 5.42.

3a Yellow solid, m.p. 98 °C. IR ($CHCl_3$) ν cm^{-1}: 3349 (NH); 1709 (C=O); 1500 (CC arom.); 1454; 1394 (C=S); 1305; 1157 (COC). ^1H NMR ($CDCl_3$) δ ppm: 1.60 (s, 9H, 3xCH_3); 4.80-4.90 (d, 1H, CH_2); 7.40 (s, 5H, Ph); 10.20 (s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ ppm: 27.70 (CH_3); 50.00 (CH_2); 84.80 ($\underline{C}Me_3$); 128.30; 129.00; 135.40 (C arom.); 158.30 (C=O); 184.90 (C=S). MS (FD) m/z: 502 ($2M^+$); 251 (M^+); 194; 149; 91. Anal. calcd for $C_{13}H_{17}NO_2S$: C, 62.10; H 6.77; N, 5.58. Found: C, 61.98; H, 6.75; N, 5.52.

3b White solid, m.p. 114 °C. IR ($CHCl_3$) ν cm^{-1}: 3310 (NH); 1710 (C=O); 1600; 1520-1500 (CC arom.); 1480; 1440; 1395 (C=S); 1302; 1158 (COC). ^1H NMR ($CDCl_3$) δ ppm: 1.56 (s, 9H, 3xCH_3); 4.81; 4.88 (d, 2H, CH_2); 6.96-8.82 (m, 4H, Pyr); 10.22 (s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ ppm: 27.73 (CH_3); 50.09 (CH_2); 84.65 ($\underline{C}Me_3$); 122.24; 122.95; 137.08; 149.17; 153.49 (C Pyr); 158.07 (C=O); 184.63 (C=S). Anal. calcd for $C_{12}H_{16}N_2O_2S$: C, 57.12; H 6.39; N, 11.10. Found: C, 56.84; H, 6.32; N, 10.90.

3c1-2 Yellow solid, m.p. 60 °C. IR (KBr) ν cm^{-1}: 1714 (C=O); 1602, 1514 (aromatic CH); 1448 (C=S); 1158 (COC). ^1H NMR ($CDCl_3$) δ ppm: **3c1** (main isomer); 1.54 (s, 9H, 3xCH_3); 3.22 (s, 3H, N-$C\underline{H}_3$); 4.69 (s, 2H, CH_2); 7.25-7.55 (m, 5H, Ph); **3c2** 1.58 (s, 9H, 3xCH_3); 3.14 (s, 3H, N-$C\underline{H}_3$); 5.15 (s, 2H, CH_2); 7.25-7.55 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$) δ ppm: **3c1** 27.88 (3x$\underline{C}H_3$): 37.61 (N-$\underline{C}H_3$); 59.43 ($\underline{C}H_2$); 84.62 ($\underline{C}Me_3$); 127.87, 128.22, 128.69, 129.01, 129.11, 133.82 (C arom.); 163.74 (C=O); 191.09 (C=S); **3c2** 27.97 (3x$\underline{C}H_3$); 39.57 (N-$\underline{C}H_3$); 54.63 ($\underline{C}H_2$); 84.52 ($\underline{C}Me_3$); 127.87, 128.22, 128.69, 129.01, 129.11, 134.30 (C arom.); 163.48 (C=O); 191.58 (C=S). MS (DCI/NH_3) m/z: 266 ($M^{+\cdot}$); 283 ($M+NH_4^+$). Anal. calcd for $C_{14}H_{19}NO_2S$: C, 63.36; H 7.22; N, 5.28. Found: C, 63.74; H, 7.24; N, 5.55.

2'g White solid, m.p. 147 °C. IR (film) ν cm^{-1}: 1735 (C=O); 1607; 1547 (CC arom., C=N); 1143 (COC). ^1H NMR ($CDCl_3$) δ ppm: 1.60 (s, 9H, 3xCH_3); 7.30-7.81 (m, 4H, Ph). ^{13}C NMR ($CDCl_3$) δ ppm: 27.95 (CH_3); 8501 ($\underline{C}Me_3$); 111.55; 121.95; 125.48; 127.74; 140.53; 150.72 (C arom.); 153.60 (-N=$\underline{C}$-O-); 155.44 (C=O). MS (DCI/NH_3) m/z: 237 ($M+NH_4^+$); 220 (MH^+); 181. Anal. calcd for $C_{12}H_{13}NO_3$: C, 65.74; H 5.98; N, 6.39; O, 21.89. Found: C, 65.68; H, 5.98; N, 6.66; O, 22.65.

Preparation of the sulfinamoyl-sulfones 4a-f and -sulfonamide 5c (method 1).

a) The starting material for **4a-f** is the commercial (Fluka) methyl phenyl sulfone. Precursor of **5c** is the N-methyl-N-phenylmethanesulfonamide Ph-N(CH_3)-SO_2CH_3 prepared by amination of the commercial chlorosulfonyl-chloride: a solution of N-methylaniline (4.71 g, 44 mmol) and triethylamine (4.44 g, 44 mmol) in anhydrous benzene (20 mL) was added dropwise at 0 °C under stirring at a solution of chlorosulfonyl methane (5.04 g, 44 mmol) in benzene (15 mL). The solution was allowed to warm at 50 °C for 10 minutes, then cooled. Chlorhydrate was filtered on Celite 245, filtrate was successively washed by dilute aqueous HCl, $HNaCO_3$ 5% aqueous solution and water. Organic layer was extracted, dried on $MgSO_4$ and solvent removed in vacuo. Expected compound was obtained as a yellow solid (m.p. = 104 °C, 70%). IR ($CHCl_3$) ν cm^{-1}: 1340 (SO_2 as); 1144 (SO_2 sym). ^1H NMR ($CDCl_3$) δ ppm: 7.40 (s, 5H, Ph); 3.35 (s, 3H, N-CH_3); 2.82 (s, 3H, CH_3).

The arylsulfinylamines ArNSO were prepared in good yields by the two already described methods: i) reaction of arylamine with thionylchloride, ii) *trans*-sulfinylation between the tosylsulfinylamine (obtained from tosylamine with $SOCl_2$) and the corresponding arylamines.[20]

The hydroxyl group of N-(2-hydroxyphenyl)sulfinylamine, precursor of **4d**, was protected by a trimethylsilyl group: a mixture of 2-OHPhNSO (10 g, 64 mmol) and TMSCl (10 g, 92 mmol) was stirred at anhydrous THF (30 mL) reflux for 2 h, then cooled and THF evaporated, along with a TMSCl excess to give the protected N-(2-trimethylsiloxyphenyl)sulfinylamine 2-OSiMe$_3$PhNSO (8.71 g, 60%). ^{1}H NMR ($CDCl_3$) δ ppm: 8.35-8 (m, 1H, Ph); 7.40-6.80 (m, 3H, Ph); 0.30 (s, 9H, 3xCH_3).

b) Condensation of Mg derivative of the sulfones or sulfonamide with an arylsulfinylamine.

A solution of CH_3SO_2-A (A = Ph, Ph-N-CH_3) (2.7 mmol), in anhydrous benzene (10 mL) was added dropwise at room temperature to stoichiometric solution of EtMgBr (prepared as described by Field[21]) in anhydrous ether (10 mL). The resulting white mixture was stirred for 10 minutes, diluted with benzene (10 mL) and warmed under reflux for few minutes. After cooling at 0 °C, ArNSO (3 mmol) in benzene (5 mL) was added dropwise under vigorous stirring. Then the icebath was removed and the mixture was stirred the whole night at room temperature and hydrolysed by a 20% NH_4Cl solution, organic layer was decanted, dried on $MgSO_4$ and solvents evaporated under vacuum; crude condensation products were purified on an open chromatographic column [silica, ether (**4a-f**) or ether/petroleum ether 80/20 (**5c**)]. Yields are given in Table 2. Deprotection of OH group of **4d** occurs during the hydrolysis process.

4a Pale yellow solid, m.p. 149 °C. IR ($CHCl_3$) ν cm^{-1}: 3280 (NH); 1325 (SO_2 as); 1145 (SO_2 sym); 1065 (SO). ^{1}H NMR ($CDCl_3$+ d_6DMSO) δ ppm: 4.45; 4.73 (AB, 2H, J = 14 Hz, CH_2); 6.80-7.80 (m, 10H, 2xPh); 8.57 (s, 1H, NH). ^{13}C NMR ($CDCl_3$+ d_6DMSO) δ ppm: 74.30 ($\underline{C}H_2$); 118.83; 123.40; 128.04; 128.43; 129.29; 129.40; 134.40; 138.99; 140.36 (C arom.). Anal. calcd for $C_{13}H_{13}NO_3S_2$: C, 52.86; H 4.44; N, 4.74. Found: C, 52.65; H, 4.44; N, 5.03.

4b Yellow solid, m.p. 161 °C. IR ($CHCl_3$) ν cm^{-1}: 3280 (NH); 1330 (SO_2 as); 1155 (SO_2 s); 1083 (SO). ^{1}H NMR ($CDCl_3$+ d_6DMSO) δ ppm: 4.38; 4.70 (AB, 2H, J = 13.8 Hz, CH_2); 6.56-6.90 (m, 4H, Cl-Ph); 7.21-7.63 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$+ d_6DMSO) δ ppm: 74.30 (CH_2); 116.05; 128.22; 130.36; 134.30; 134.57; 138.82 (C of Cl-Ph); 117.86; 122.77; 129.19; 142.02 (C of Ph). Anal. calcd for $C_{13}H_{12}NO_3S_2Cl$: C, 47.37; H 3.67; N, 4.25. Found: C, 47.63; H, 3.71; N, 3.93.

4c Pale yellow solid, m.p. 143 °C. IR (KBr) ν cm^{-1}: 3195 (NH); 1305 (SO_2 as); 1145 (SO_2 s); 1065 (SO). ^{1}H NMR ($CDCl_3$+ d_6DMSO) δ ppm: 4.71; 4.98 (AB, 2H, J = 4 Hz, CH_2); 6.97-7.87 (m, 10H, 2xPh). ^{13}C NMR ($CDCl_3$+ d_6DMSO) δ ppm: 73.98 (CH_2); 116.50; 126.05; 126.12; 127.62; 127.85; 128.86; 133.96; 138.55; 144.10 (C of Ph and Cl-Ph). Anal. calcd for $C_{13}H_{12}NO_3S_2Cl$: C, 47.37; H 3.67; N, 4.25. Found: C, 47.31; H, 3.55; N, 4.10.

4d Sticky liquid. IR ($CHCl_3$) ν cm^{-1}: 3430 (OH); 3300-3240 (NH); 1330 (SO_2 as); 1155 (SO_2 s); 1082 (SO). ^{1}H NMR ($CDCl_3$) δ ppm: 4.48; 4.76 (d, AB, J = 14 Hz, CH_2); 6.80-8.00 (m, 11H, HO-Ph-NH, Ph). Anal. calcd for $C_{13}H_{13}NO_4S_2$: C, 50.15; H 4.21; N, 4.50. Found: C, 50.45; H, 4.11; N, 4.25.

4e Orange solid, m.p. 205 °C. IR (KBr) ν cm^{-1}: 3130 (NH); 1515, 1305 (NO_2); 1342 (SO_2 as); 1155 (SO_2 s); 1068 (SO). ^{1}H NMR ($CDCl_3$+ d_6DMSO) δ ppm: 4.38; 4.60 (AB, 2H, J = 13.6 Hz, CH_2); 6.55-7.25 (m, 5H, Ph); 7.42-7.66 (m, 4H, O_2N-Ph); 9.58 (s, 1H, NH). ^{13}C NMR ($CDCl_3$+ d_6DMSO) δ ppm: 78.83 (CH_2); 113.27; 118.53; 124.80; 125.92; 127.90; 128.44; 128.55; 128.97; 129.10; 134.07; 143.20; 153.62 (C of Ph and O2NPh). Anal. calcd for $C_{13}H_{12}N_2O_5S_2$: C, 45.87; H 3.55; N, 8.23. Found: C, 45.67; H, 3.81; N, 7.98.

4f Yellow solid, m.p. 213 °C. IR (KBr) ν cm^{-1}: 3304 (NH); 1326 (SO_2 as); 1148 (SO_2 s); 1069 (SO). ^{1}H NMR ($CDCl_3$+ d_6DMSO) δ ppm: 4.46; 4.71 (AB, 2H, J = 11 Hz, CH_2); 6.69-7.00 (m, 4H, CF_3-Ph); 7.32-7.71 (m, 5H, Ph); 8.86 (s, 1H, NH). ^{13}C NMR ($CDCl_3$+ d_6DMSO) δ ppm: 78.83 (CH_2); 113.27; 118.53; 124.80; 125.92; 127.90; 128.44; 128.55; 128.97; 129.10; 134.07; 143.20; 153.62 (C of Ph and O_2N-Ph). Anal. calcd for $C_{14}H_{12}NO_3S_2F_3$: C, 46.28; H 3.33; N, 3.85. Found: C, 46.05; H, 3.31; N, 3.80.

5c Yellow solid, m.p. = 108 °C. IR ($CHCl_3$) ν cm^{-1}: 3290 (NH); 1335 (SO_2 as); 1145 (SO_2 s); 1078 (SO). ^{1}H NMR ($CDCl_3$+ d_6DMSO) δ ppm: 3.42 (s, 3H, CH_3); 4.29; 4.41 (AB, 2H, J = 13.8 Hz, CH2); 7.04-7.46 (m, 11H, 2xPh and NH). ^{13}C NMR ($CDCl_3$+ d_6DMSO) δ ppm: 39.16 (CH_3); 66.57 (CH_2); 119.83; 124.48; 127.34; 128.35; 129.70; 139.49; 140.14 (C of 2xPh). Anal. calcd for $C_{14}H_{16}N_2O_3S_2$: C, 51.83; H 4.97; N, 8.63. Found: C, 52.15; H, 4.97; N, 8.26.

Preparation of sulfinamoylsulfonamides 5a-b (method 2).

a) The precursor N-phenylmethanesulfonamide Ph-NH-SO_2CH_3 was prepared as previously described for the methylated analog, by condensation of chloromethylsulfone and aniline in triethylamine. Yield 60%. m.p. 94 °C. IR ($CHCl_3$) ν cm^{-1}: 3260 (NH); 1350 (SO_2 as); 1150 (SO_2 sym).

b) Condensation of sulfinylaniline with the dilithium derivative of Ph-NH-SO_2CH_3. A solution of n-butyllithium in hexan (1.6 M, 4 mL, 6.4 mmol) was added dropwise with a syringe at -78 °C under dry nitrogen to diisopropylamine (1 mL, 7 mmol) in anhydrous THF (5 mL) and mixture stirred for 1/2 h. Then, a solution of $PhNHSO_2CH_3$ (0.5 g, 3 mmol) in THF (10 mL) was added dropwise at the same temperature. After 1 1/2 h, a solution of sulfinylaniline (0.45 g, 3.3 mmol) was quickly added dropwise at -78 °C to the dilithiated

sulfonamide derivative and stirred at this temperature for the whole night. Mixture was gently warmed at 0 °C and hydrolysed with a 20% NH_4Cl solution (20 mL). The extraction was achieved by an acidic solution (pH 4). The organic layer was dried on $MgSO_4$ and solvents evaporated, under vacuum, to give crude sticky liquids which slowly crystallise. Recrystallisation were performed in ether to afford purified **5a** and **5b**. Characteristics are given below and in Table 2.

5a Yellow solid, m.p. 157 °C. IR (KBr) ν cm^{-1}: 3305; 3140 (NH); 1350 (SO_2 as); 1145 (SO_2 s); 1070 (SO). ^1H NMR ($CDCl_3$+ d_6DMSO) δ ppm: 4.60 (s, 2H, CH_2); 6.90-7.30 (m, 10H, 2xPh and NH); 8.76 (s, 1H, NH-Ph). Anal. calcd for $C_{13}H_{14}N_2O_3S_2$: C, 50.31; H 4.55; N, 9.03. Found: C, 50.17; H, 4.55; N, 8.98.

5b Yellow solid, m.p. 140 °C. IR (KBr) ν cm^{-1}: 3313 (NH); 3158 (NHSO$_2$); 1345 (SO_2 as); 1146 (SO_2 s); 1075 (SO). ^1H NMR ($CDCl_3$+ d_6DMSO) δ ppm: 4.33; 4.42 (AB, 2H, J = 13.2 Hz, CH_2); 6.77-7.13 (m, 9H, Ph and Cl-Ph); 8.85 (s, 1H, NH-Ph); 9.35 (s, 1H, NH-PhCl). ^{13}C NMR ($CDCl_3$+ d_6DMSO) δ ppm: 68.8 (CH_2); 116.55; 121.4; 125.13; 130.41; 134.75; 136.80 (C of Cl-Ph); 118.40; 123.01; 129.32; 142.10 (C of Ph). Anal. calcd for $C_{13}H_{13}N_2O_3S_2Cl$: C, 45.28; H 3.80; N, 8.12. Found: C, 44.93; H, 3.75; N, 7.96.

Preparation of the sulfines 6a and 6b.

a) The synthesis of t-butylchlorosulfinyl acetate (R = H) and propanoate (R = CH_3), ClSOCHRCOOtBu was made in two steps (scheme 4) according to the method of Kee and Douglas,[22] adapted to the preparation of sulfinamoyl esters.[2b] Total yield (83%, R = H, 60%, R = CH_3).

$ClSOCH_2CO_2tBu$, yellow oil. IR (KBr) ν cm^{-1}: 1725 (C=O); 1145 (COC); 1122 (Sh, SO). ^1H NMR ($CDCl_3$) δ ppm: 1.45 (s, 9H, 3xCH_3); 4.20 (s, 2H, CH_2). ^{13}C NMR ($CDCl_3$) δ ppm: 27.90 (CH_3); 68.90 (CH_2); 84.60 ($\underline{C}Me_3$); 166.00 (C=O).

$ClSOCH(CH_3)CO_2tBu$, yellow oil. IR (KBr) ν cm^{-1}: 1746 (C=O); 1155 (COC); 1122 (SO). ^1H NMR ($CDCl_3$) δ ppm: 1.41; 1.51 (d, 3H, J = 7 Hz, $C\underline{H}_3$-CH); 1.51 (s, 9H, 3xCH_3); 4.04 (q, 1H, J = 7 Hz, CH_3-C$\underline{H}$). ^{13}C NMR ($CDCl_3$) δ ppm: 27.70 (CH_3); 28.10 ($\underline{C}H_3$-CH); 53.60 (CH_3-$\underline{C}$H); 84.60 ($\underline{C}Me_3$); 165.50 (C=O).

b) Sulfines O=S=CR-COOtBu were obtained by dehydrohalogenation of above chlorosulfinyl compounds in basic medium.

A solution of 8 mmol of chlorosulfinyl ester in anhydrous ether (5 mL) was added dropwise at -30 °C under stirring to a solution of Et_3N (0.97 g, 9.6 mmol) in anhydrous ether (10 mL). Then the chlorhydrate was filtered and 2 times rinsed with diethyl ether. The filtrate was evaporated and the residue eventually kept in a chloroformic solution.

6a (R = H) was left in solution. IR ($CHCl_3$) ν cm^{-1}: 1728 (C=O); 1300 (SO_2, dimer); 1149 (COC); 1110 (SO) monomer). MS (DCI/NH_3) m/z: 342 (2M + NH_4^+); 325 ($2MH^+$); 180 (M^+ + NH_4^+); 163 (MH^+).

6b (R = CH_3) was isolated as a yellow oil after purification by HPLC (Et_2O 100%), yield 62%. IR (film) ν cm^{-1}: 1725 (C=O); 1150 (COC); 1105 (SO). ^1H NMR ($CDCl_3$) δ ppm: 1.42 (s, 9H, 3xCH_3); 1.47 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ ppm: 27.30 (CH3); 27.90 (3xCH_3); 83.60 ($\underline{C}Me_3$); 162.4 (C=O); 184.4 (C=S). MS (DCI/NH_3) m/z: 194 (M + NH_4^+); 128; 103.

Trapping of an intermediate sulfine to cycloadduct **7**, Diels-Alder type, between sulfinamoyl ester **1c** and 2,3-dimethylbuta-1,3-diene. The t-butyl para-chlorophenylsulfinamoyl acetate (0.3 g, 1.036 mmol), 2,3-dimethylbuta-1,3-diene (1.1 equivalent, 0.093 g) and a catalytic quantity of Et_3N (0.1 equivalent, 0.010 g) were heated in solvent toluene at 65 °C for 6 hours. After solvent evaporation under vacuum, residue was purified on silica gel chromatography (ether) to give the expected cycloadduct **7** (0.101 g, 40%).

IR ($CHCl_3$) ν cm^{-1}: 1724 (C=O); 1152 (COC). ^1H NMR ($CDCl_3$) δ ppm: 1.43 (s, 9H, 3xCH_3); 1.67 (s, 6H, 2xCH_3); 3.03, 3.23 (d, AB, J = 16.6 Hz, CH_2); 2.45 (A), 2.67 (B), 3.71 (X) (dq and dd, ABX, J_{AB} = 18 Hz, J_{AX} = 7 Hz, J_{BX} = 4.5 Hz, CH_2-CH). ^{13}C NMR ($CDCl_3$) δ ppm: 19.61, 19.90 (2x$\underline{C}H_3$); 27.95 (3x$\underline{C}H_2$); 62.15 ($\underline{C}$H); 83.17 ($\underline{C}Me_3$); 117.04; 126.66 (2xC=); 167.54 ($\underline{C}$=O). MS (DCI/NH_3) m/z: 245 ($MH^{+\cdot}$); 262 (M+NH_4^+); 489 (2M+H^+).

Aminolysis of sulfinamoyl-sulfone 4a and -sulfonamides 5a,c. The protocol already described for sulfinamoyl esters **1** aminolysis was used. Typically, an excess of imidazole (4 equivalents) in CH_3CN (15 mL) was added at 25 °C to a solution of **4a** in CH_3CN (15 mL). The progress of the reaction was controlled by TLC on silicagel (ethyl acetate/petroleum ether 50/50). After 2 h, substrate had disappeared, solvent was evaporated. The residue purified by open chromatography column using ethyl acetate/petroleum ether 30/70, affords N,N'-diphenylthiourea **8a** with quantitative yield. In the same way, sulfonamide **5a** with imidazole at 25 °C for 2 h gives N,N'-dibenzylthiourea **8b**, but no reaction was observed at 0 °C. Physical and spectroscopic data of **8a,b** are in good agreement with the literature data:. melting point **8a** 153 °C, **8b** 149 °C and mass peak (EI, $M^{+\cdot}$) m/z : **8a**, 228; **8b**, 256.

Computational details. All structures were optimized with the Gaussian 94 program.[23] Pseudopotentials[24] were used for the core electrons of carbon, oxygen and sulfur. Valence basis sets of contracted Gaussian functions are of double-zeta quality with d polarization functions added on carbon ($\zeta = 0.80$), oxygen ($\zeta = 0.85$) and sulfur ($\zeta = 0.54$).

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