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SYNTHESIS OF THIOOXAMATES FROM t-BUTYL SULFINAMOYL ACETATES. OCCURRENCE OF A NEW REARRANGEMENT INVOLVING A THIONE S-IMIDE INTERMEDIATE

BALTAS M., CAZAUX L., de BLIC A., GORRICHON L. and TISNES P.

Laboratoire de Synthèse et Physicochimie Organique associé au CNRS
Université Paul Sabatier - 118, route de Narbonne 31062 TOULOUSE CEDEX (FRANCE)

SUMMARY : Reactions of t-butyl sulfinamoylacetates with amines yield, via a new rearrangement in sulfur chemistry, thiooxamates with or without substitution of the amine moiety of the substrate, depending on the nature of the reacting amine.

Previous work [1] on t-butyl sulfinamoyl acetates demonstrated that these compounds are efficient and specific inhibitors of the coniferyl alcohol dehydrogenase CADH (EC 1.1.1.4.). This zinc-containing metalloenzyme and its NADH cofactor are involved in the last step of the biosynthesis of lignin monomers through the reduction of coniferaldehydes to the corresponding alcohols.

Many similarities with several zinc-metalloenzymes (LADH, carboxypeptidase A...) where a reactive water molecule is bound at the metal [2], prompted us to study the complexation [3a] and the hydrolysis [3b] of t-butyl sulfinamoylacetates. In addition, the primary structure of the CADH shows [4] that thiol (from cysteine) and imidazole (from histidine) groups are present at the active site. In connection with these findings we report here the reactivity of some t-butyl sulfinamoyl acetates with amines.

t-Butyl sulfinamoylacetates react at room temperature in acetonitrile or ethyl 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: ether80:20) to give thioxamates in fair to good yields (table 1). They are characterized by analytical and spectroscopic methods[5].

Thiooxamates obtained are greatly dependent on the nature of the amine (scheme 1).

Scheme 1

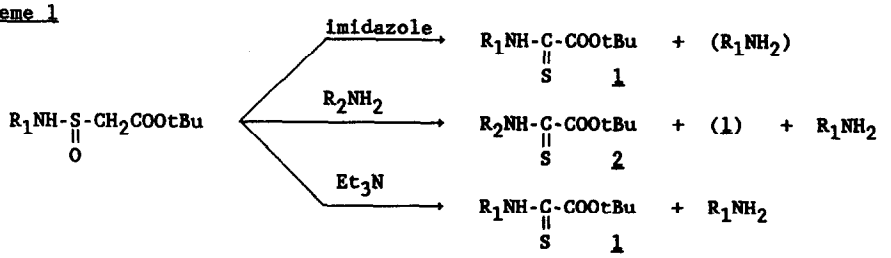


TABLE 1 - Reaction of t-butyl sufinamoyl acetates $R_1NHS(O)CH_2C(O)OtBu$ with various amines

Entry	R_1	Amine	Solvent	Reaction time(h)	Product	Yield %	R_1NH_2 recovered %
1	C_6H_5	imidazole	CH_3CN	72	1a	86	5
2	3-ClC_6H_4	imidazole	CH_3CN	36	1b	65	10
3	4-$OMeC_6H_4$	"	"	"	1c	73	5
4	C_6H_{11}	"	"	"	1d	60	10
5	C_6H_5	$PhCH_2NH_2$	"	"	2a	45	100
			Et_2O	72	2a	63	100
6	4-$NO_2C_6H_4$	"	Et_2O	48	2a	41	100
7	3-ClC_6H_4	"	"	72	2a	43	100
8	C_6H_5		CH_3CN	36	2b+(1a)	35(9)	56
9	C_6H_5	Et_3N	CH_3CN	36	1a	25	45

Thiooxamates RNHC(S)C(O)OtBu

	R = R_1		R = R_2
1a	C_6H_5	2a	$C_6H_5CH_2$
1b	3-ClC_6H_4	2b	
1c	4-$OMeC_6H_4$		
1d	C_6H_{11}		

With a weak secondary amine such as imidazole (pK_A = 7.2) the product 1 results from a rearrangement of the starting sulfinamoyl acetate with a loss of a water molecule ; the overall effect of the amine is a general catalysis (table 1, entries 1-4).

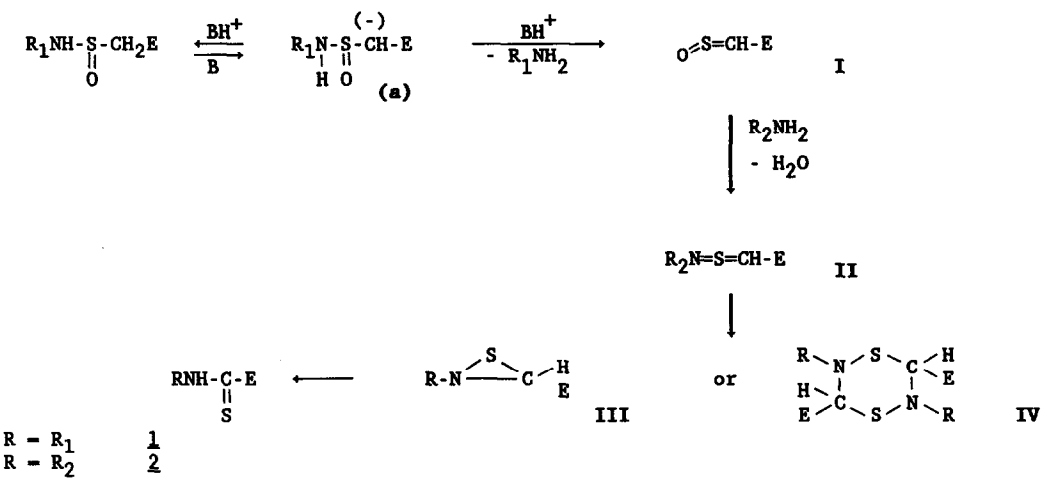
With a strong primary amine such as benzylamine (pK_A = 9.33) the nature of thiooxamate 2a reveals an amine group substitution indicating the participation of the amine as a nucleophile. This substitution is also illustrated by the quantitative recovery of the arylamine liberated from the sulfinamoyl acetate (table 1, entries 5-7) while it is very poor when the amine is imidazole. The field desorption mass spectrum of compound 2a presents along with the characteristic tropylium ion (m/e = 91) two peaks, one at m/e = 251 corresponding to the thiooxamate 2a, the other at m/e = 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 (pK_A = 8.65) is used a mixture of both thiooxamates 1 and 2 is obtained and aniline is recovered at 56% yield (table 1, entry 8).

Finally the reaction with a strong tertiary amine (triethylamine pK_A = 11.0) gives the thiooxamate 1 in a modest yield while the amount of aniline is greatly increased (table 1 entry 9).

All these results can be rationalised taking into account the following scheme.

Scheme 2 R = COOtBu



In a first step a methylenic proton activated by the ester and the sulfinyl group is abstracted by the amine leading to the conjugate base of the substrate which decomposes to an intermediate sulfine I, as we observed for the basic hydrolysis of these compounds [3b]. This sulfine then reacts either with the leaving amine R_1NH_2 either with the added amine R_2NH_2 or both following the strenght of the base to give thione S-imide II. This latter intermediate gives then the cyclic sulfenamides III or IV which upon proton transfer and N-S bond fission rearrange yielding the corresponding thiooxamates 1 and 2. Thione S-imides are known as reaction intermediates [7a] or stable compounds [7b]. Nevertheless in all the quoted cases, these compounds are lacking an hydrogen atom at the sp^2 carbon or the nitrogen atom of the thione S-imide function. They have been also reported as precursors of cyclic three membered sulfenamides which undergo desulfurization to yield imines [7a]. A carbophilic attack of the amine on the intermediate sulfine, yielding after elimination of a water molecule the final thiooxamate seems improbable. Zwanenburg [8] pointed out that such a carbophilic reaction may be particularly envisaged when the sulfine carbon atom bears a potential leaving group such as Cl^-, PhS^-....

When the two methylenic protons of the starting sulfinamoylacetates are substituted by two methyl groups no reaction with amines is observed, as we noticed for water in the base hydrolysis reaction [3b]. This result indicates the determinant role of the first deprotonation equilibrium for the reactivity of sulfinamoylacetates.

It is noteworthy that when the basicity of primary amines is reduced the two types of thiooxamates 1 and 2 are formed.

In conclusion the reactions described above present a new type of rearrangement in sulfur chemistry involving a thione S-imide intermediate. They also constitute a new and facile method for the synthesis of thiooxamates diversely substituted on the nitrogen atom. On-

ly few accesses to thiooxamates are known until now [8,9] and their application is patented as gametocides in plants.

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5 - **1a** : oil ; IR($CHCl_3$) 3310, 1705, 1595, 1530-1490, 1390, 1370, 1305, 1155 cm^{-1} ; ^1H NMR ($CDCl_3$) ; δ 1.61 (s, 9H), 7.10-8,10 (m, 5H), 10.60 (s, 1H) ; ^{13}C NMR ($CDCl_3$) δ 27,71, 85, 36, 121.99, 127.23, 129.11, 137.91, 158.5, 180.99 ; M.S. (E.I) 237 ($M^{+\bullet}$), 181, 136, 101, 77, 57.

1b : oil ; IR ($CHCl_3$) 3311, 1706, 1589, 1522, 1479, 1375, 1305, 1155 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 1.60 (s, 9H), 7.20-8.14 (m, 4H), 10.54 (m, 1H) ; ^{13}C NMR ($CDCl_3$) δ 27.67, 65.58, 120.14, 121.85, 127.19, 130.10, 134.69, 138.96, 158.24, 181.51 ; M.S. (E.I.) 273, 271 ($M^{+\bullet}$), 113, 111, 57.

1c : oil; IR ($CHCl_3$), 3320, 1705, 1610, 1515, 1463, 1395, 1375, 1305, 1157 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 1.60 (s, 9H), 3.81 (s, 3H), 6.90-7.00 and 7.80-7.90 (m, 4H), 10.56 (s, 1H) ; ^{13}C NMR ($CDCl_3$) δ 27.69, 55.62, 85.15, 114.09, 123.77, 131.06, 158.24, 158.33, 180.30 ; M.S. (E.I.) 267 ($M^{+\bullet}$), 211, 166, 108, 92, 77, 57.

1d : oil ; IR ($CHCl_3$) 3338, 1706, 1510, 1453, 1397, 1369, 1296, 1156 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 1.20-2.10 (m, 19H), 4.14-4.35 (m, 12H), 8.80 (s, 1H) ; ^{13}C NMR ($CDCl_3$) δ 24.53, 25.42, 27.66,30.69, 54.11, 64.72, 158.54, 183.04 ; M.S. (E.I.) 243 ($M^{+\bullet}$), 188, 187, 169, 112, 83, 57.

2a : mp : 98°C ; IR ($CHCl_3$) 3349, 1709, 1500, 1454, 1394, 1372, 1305, 1157 cm^{-1}, ^1H NMR ($CDCl_3$) δ 1.60 (s, 9H), 4.80-4.90 (d, 1H), 7.40 (s, 5H), 10.20 (s, 1H) ; ^{13}C NMR ($CDCl_3$) δ 27.7, 50.0, 84.8, 128.3, 129.0, 135.4, 158.3, 184.9, M.S. (FD) 502 ($2M^+$), 251 (M^+), 194, 149, 91.

2b : mp = 114°C ; IR ($CHCl_3$) 3310, 1710, 1600, 1520-1500, 1480, 1440, 1395, 1372, 1302, 1158 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.56 (s, 9H), 4.81, 4.88 (d, 2H), 6.96-8.82 (m, 4H), 10.22 (s, 1H) ; ^{13}C NMR ($CDCl_3$) δ 27.73, 50.09, 84.65, 122.24, 122.95, 137.08, 149.17, 153.49, 158.07,184.63.
Satisfactory elemantary analysis (± 0,3%) were obtained for all compounds.

6 - Cyclic structure IV of scheme 2 can be postulated for the dimeric form. Few analogous compounds are quoted in the literature as stable but all are lacking hydrogen atom on the carbon of the six membered heterocycle.
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