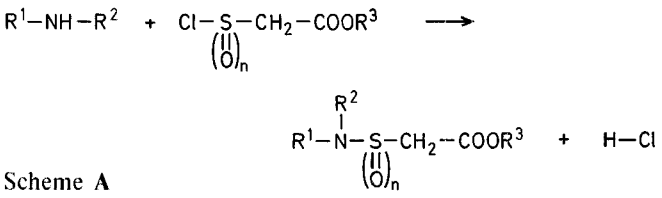
A Convenient and Facile Synthesis of β-Aminosulfinyl- and β-Aminosulfonylalkanoic Esters from Metallated Esters and *N*-Sulfinylamines

Arnaud DE BLIC, Louis CAZAUX*, Liliane GORRICHON-GUIGON, Marcel PERRY

Equipe de Recherche Associée au C.N.R.S. no. 686, Synthèse et Physicochimie Organique, Université Paul Sabatier, 118 route de Narbonne, F-31062 Toulouse Cedex, France

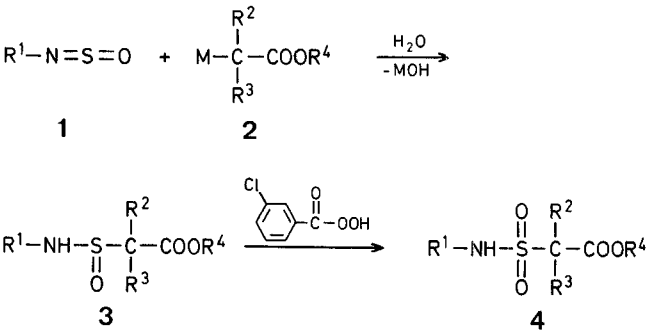
In order to examine the mechanisms of zinc-containing enzymes and to reduce or inhibit their activity, linear sulfur derivatives able to present some metal-binding sites such as β-aminosulfinyl- and β-aminosulfonylalkanoic esters have been synthesised[1]. Previously reported β-aminothio (n = 0) and β-aminosulfonyl (n = 2) esters were usually prepared[2-7] by reaction of an amine with a sulfenyl or sulfonyl chloride following Scheme **A**.



Scheme **A**

Only one example[2] of the preparation of a β-aminosulfinyl ester (n = 1) was reported involving the oxidation of a β-aminothio ester [n = 0, $R^1 = H_3C{-}CO$, $R^2 = Si(CH_3)_3$; $R^3 = C_2H_5$]. On the other hand, many papers[3-7] describe the preparation of β-aminosulfonyl esters and some corresponding acids. Starting from different compounds, all the methods involve, as a common step, the formation of a sulfonyl chloride.

Here, we report a convenient and easy route to both β-aminosulfinyl esters and β-aminosulfonyl esters: condensation of an *N*-sulfinylamine **1** with bromozinc (**2**; M = BrZn) or lithium ester enolate (**2**; M = Li), followed by hydrolysis with aqueous ammonium chloride gives with good yield the β-aminosulfinyl compound **3** (Scheme **B**), which is readily oxidised to the β-aminosulfonyl ester **4**.



M = ZnBr, Li

Scheme **B**

The Reformatsky reaction was preferred (Method A) whenever the bromozinc ester **2** was easily available; otherwise the lithium ester enolate **2** was prepared using *n*-butyllithium and

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Table 1. β-Aminosulfinylalkanoic Esters **3**

Product No.	R^1	R^2	R^3	R^4	Method	Yield [%]	m.p. [°C]	Molecular formula[a]	I.R. (CCl_4) ν [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$/TMS, 60 MHz) δ [ppm]
3a	C_6H_5	H	H	*t*-C_4H_9	A	93	103°	$C_{12}H_{17}NO_3S$ (255.3)	3160 (NH); 1725 (C=O); 1155 (COC); 1065 (SO)	1.47 (s, 9H); 3.90 (s, 2H); 6.9–7.4 (m, 5H); 7.53 (s, 1H)
3b	C_6H_5	CH_3	H	*t*-C_4H_9	A	91	99°	$C_{13}H_{19}NO_3S$ (269.4)	3150 (NH); 1725 (C=O); 1150 (COC); 1065 (SO)	1.45, 1.50 (2 s, 9H); 1.53, 1.56 (2 d, 3H, J=7.7 Hz); 3.80, 3.92 (2 q, 1H, J=7.7 Hz); 6.8–7.5 (m, 6H)
3c	C_6H_5	CH_3	CH_3	*t*-C_4H_9	B	85	122°	$C_{14}H_{21}NO_3S$ (283.4)	3280, 3180 (NH); 1735 (C=O); 1150 (COC); 1090 (SO)	1.47 (s, 9H); 1.53 (s, 6H); 6.40 (s, 1H); 6.9–7.5 (m, 5H)
3d	C_6H_5	CH_3	CH_3	C_2H_5	A	86	82°	$C_{12}H_{17}NO_3S$ (255.3)	3270, 3180 (NH); 1740 (C=O); 1150 (COC); 1095 (SO)	1.25 (t, 3H, J=7 Hz); 1.57 (s, 6H); 4.22 (q, 2H); 6.57 (s, 1H); 6.8–7.3 (m, 5H)
3e	*c*-C_6H_{11}	H	H	*t*-C_4H_9	A	50	67°	$C_{12}H_{23}NO_3S$ (261.4)	3260, 3170 (NH); 1730 (C=O); 1160 (COC); 1075 (SO)	1.50 (s, 9H); 0.7–2.2 (m, 10H); 3.40, 3.50 (AB-q, 2H); 2.9–3.5 (m, 1H); 4.68 (d, 1H, J=6 Hz)
3f	*c*-C_6H_{11}	CH_3	H	*t*-C_4H_9	A	95	oil	$C_{13}H_{25}NO_3S$ (275.4)	3290 (NH); 1730 (C=O); 1150 (COC); 1080 (SO)	1.0–2.2 (m, 10H); 1.38, 1.42 (2 d, 3H, J=6 Hz); 1.50 (s, 9H); 2.8–3.7 (m, 1H); 3.43, 3.60 (2q, 1H, J=6 Hz); 4.28, 4.33 (2 d, 1H, J=6 Hz)
3g	*c*-C_6H_{11}	CH_3	CH_3	C_2H_5	A	93	oil	$C_{12}H_{23}NO_3S$ (261.4)	3300 (NH); 1735 (C=O); 1150 (COC); 1080 (SO)	1.27 (t, 3H, J=7 Hz); 1.43 (s, 3H); 1.47 (s, 3H); 1.0–2.2 (m, 10H); 2.8–3.5 (m, 1H); 3.93 (d, 1H); 4.20 (q, 2H, J=7 Hz)

[a] Satisfactory microanalyses obtained: C ±0.36, H ±0.32, N ±0.20.

Table 2. β-Aminosulfonylalkanoic Esters **4**

Product No.[a]	Yield [%]	m.p. [°C]	Molecular formula[b]	I.R. (CCl_4) [cm^{-1}] ν_{NH}	$\nu_{C=O}$	$\nu_{SO_2\text{-asym}}$	ν_{COC}	$\nu_{SO_2\text{-sym}}$	^{1}H-N.M.R. ($CDCl_3$/TMS, 60 MHz) δ [ppm]
4a	85	93–94°	$C_{12}H_{17}NO_4S$ (271.3)	3340, 3260	1730	1350	1165	1110	1.50 (s, 9H); 3.87 (s, 2H); 7.10 (s, 1H); 7.3–7.4 (m, 5H)
4b	85	104°	$C_{13}H_{19}NO_4S$ (285.4)	3340, 3260	1730	1350	1155	1130	1.50 (s, 9H); 1.53 (d, 3H, J=7 Hz); 3.93 (q, 1H, J=7 Hz); 7.10 (s, 1H); 7.2–7.4 (m, 5H)
4c	52	61°	$C_{14}H_{21}NO_4S$ (299.4)	3350, 3250	1740, 1710	1345	1150	1120	1.43 (s, 9H); 1.53 (s, 6H); 7.25–7.4 (m, 5H); 8.69 (s, 1H)[c]
4d	90	66°	$C_{12}H_{17}NO_4S$ (271.3)	3350, 3250	1740, 1720	1350	1165	1125	1.27 (t, 3H, J=7 Hz); 1.60 (s, 6H); 4.21 (q, 2H, J=7 Hz); 7.13 (s, 1H); 7.2–7.4 (m, 5H)
4e	66	111°	$C_{12}H_{23}NO_4S$ (277.4)	3370, 3280	1730	1340	1160	1100	1.51 (s, 9H); 0.9–2.1 (m, 10H); 3.1–3.6 (m, 1H); 3.93 (s, 2H); 4.92 (d, 1H, J=8 Hz)
4f	51	82°	$C_{13}H_{25}NO_4S$ (291.4)	3395, 3270	1730	1330	1160	1120	1.51 (s, 9H); 1.60 (d, 3H, J=7 Hz); 0.9–2.2 (m, 10H); 3.0–3.6 (m, 1H); 3.90 (q, 1H, J=7 Hz); 4.95 (d, 1H, J=8 Hz)
4g	95	oil	$C_{12}H_{23}NO_4S$ (277.4)	3395, 3270	1730	1325	1160	1120	1.15 (t, 3H); 1.67 (s, 6H); 1.1–2.2 (m, 10H); 3.1–3.6 (m, 1H); 4.28 (q, 2H, J=7 Hz); 4.77 (d, 1H, J=8 Hz)

[a] For R^1, R^2, R^3, R^4, see Table 1.
[b] Satisfactory microanalyses obtained: C ±0.44, H ±0.25, N ±0.38; exception: **4a**, C −0.57.
[c] $CDCl_3$/DMSO-d_6 solution.

diisopropylamine (Method B). The two methods lead to roughly the same high yields of the prepared compounds **3** (based on **1**), see Table 1.

Starting from *t*-butyl bromopropanoate, two diastereoisomers of the *t*-butyl 2-aminosulfinylpropanoates **3b** and **3f** were obtained, related to the chirality of the carbon atom in the α-position of the ester group. ^{1}H-N.M.R. analysis of the methyl signals of the two isomer pairs shows an approximate 50/50 ratio. No separation was observed by analytical methods and attempts to effect separation were unsuccessful.

β-Aminosulfinyl esters **3** were oxidised with 1.5 equivalents of *m*-chloroperbenzoic acid in chloroform at 0°C during 1 to 3 h, then purified by washing with 5% aqueous sodium hydrogen carbonate[8]. Usually, very good yields of the β-aminosulfonyl esters **4** are obtained except for **4c** whose separation was more difficult (Table 2).

The present method is an efficient preparation of β-aminosulfonyl esters **4** under mild reaction conditions and a good access to the little-known class of β-aminosulfinyl esters **3**.

N-Sulfinylamines **1** were prepared by action of thionyl chloride on an amine alone (R^1 = phenyl)[9] or in presence of quinoline (R^1 = cyclohexyl)[10] and distilled under vacuum. Bromoesters are commercial compounds or were prepared from the appropriate bromoacid bromide and alcohol[11].

β-Aminosulfinyl Esters 3; General Procedures:

Method A: t-*Butyl Phenylaminosulfinylacetate* **(3a):**

The Reformatsky reagent **2** is prepared according to Ref.[12] from freshly made zinc chips (2.9 g, 44 mmol) and *t*-butyl bromoacetate (7.8 g, 40 mmol) in dry dimethoxymethane (50 ml). *N*-sulfinylaniline (3 g, 22 mmol) in dimethoxymethane (20 ml) is then added quickly at room temperature. The mixture is stirred for a maximum of 10 min to avoid side reactions. The mixture is then hydrolysed with 20% aqueous ammonium chloride solution (100 ml) and extracted with ether. The white precipitate (93% yield) is recrystallised from 30/70 ether/petroleum ether to give pure **3a**; yield: 4.6 g (84%); m.p. 103°C.

$C_{12}H_{17}NO_3S$	calc.	C 56.45	H 6.71	N 5.49
(255.3)	found	56.31	7.03	5.37

Method B: t-*Butyl 2-Phenylaminosulfinyl-2-methylpropanoate* **(3c):**

The lithium ester enolate **2** is preformed according to Ref.[13] from 1.6 molar *n*-butyllithium in hexane (15 ml, 24 mmol), diisopropylamine (3 g, 30 mmol), and *t*-butyl 2-methylpropanoate (3.5 g, 24 mmol) at 0°C in dry pentane (50 ml). The mixture is stirred for 1 h and evaporated to dryness. Benzene (70 ml) is added followed by rapid addition of *N*-sulfinylaniline (3 g, 22 mmol) in benzene (5 ml). The mixture is stirred for 2–5 min and worked up as in Method A to give a white solid which is recrystallised from 30/70 ether/petroleum ether; yield: 5.2 g (85%); m.p. 122°C.

$C_{14}H_{21}NO_3S$	calc.	C 59.34	H 7.47	N 4.94
(283.4)	found	59.16	7.61	5.06

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