Tetrahedron Vol 44, No. 4, pp. 1153 to 1158, 1988
Printed in Great Britain.

0040-4020/88 $3.00+.00

THE INVENTION OF RADICAL REACTIONS. PART XVII. A DECARBOXYLATIVE SULPHONYLATION OF CARBOXYLIC ACIDS

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(*Received in Belgium* 27 *November* 1987)

Abstract - *Irradiation with visible light of N-hydroxy-2-thiopyridone esters 1 in the presence of sulphur dioxide gave the corresponding thiosulphonates 4 in good yield. These could be converted to sulphones 5 by treatment with KOH and an alkylating agent. Alternatively, exposure to sulphuryl chloride followed by a primary or secondary amine afforded sulphonamides 6.*

The carboxylic acid function is present in many classes of natural compounds, some of which are of paramount biological importance. These include the amino acids, the bile acids, prostaglandins and leukotrienes, to name but a few. The possibility of manipulating this ubiquitous functional group under mild conditions should therefore open up new vistas in terms of partial syntheses and improved biological activity profiles.

Over the past few years, we have shown that N-hydroxy-2-thiopyridone esters 1 of carboxylic acids are useful in this regard.[1] Heating or (better) irradiation with visible light causes a decarboxylative rearrangement to occur proceeding by way of the radical chain mechanism depicted in Scheme 1 (path A). The utility of this process arises from the ease with which the intermediate carbon radical is intercepted allowing an array of synthetically valuable modifications.[1]

In this paper, we present a simple procedure for exchanging a carboxylic group for a sulphonic acid derived functionality. This work was spurred by the potential pharmacological utility of converting a biologically active carboxylic acid into the corresponding sulphonamide (cf. the inhibitory activity of sulphanilamide in p-aminobenzoic acid metabolism in bacteria).[2] Such a conversion can, in principle, be accomplished by first capturing the carbon radical with sulphur dioxide. The sulphonyl radical thus produced would propagate the chain by reacting with the thiocarbonyl group of the starting ester to give ultimately thiosulphonate 4 (Scheme 1, path B). The latter can then act as a springboard for a variety of further transformations.

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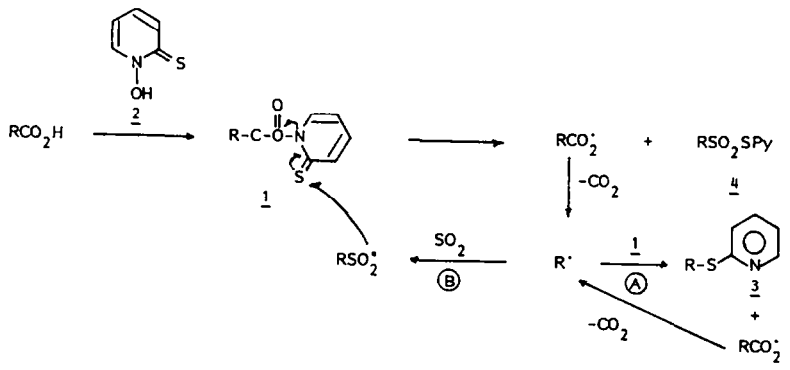


Scheme 1

The addition of carbon radicals onto sulphur dioxide does not seem to have attracted much attention. In the somewhat sparse published work, carbon radicals generated photochemically,[3a] by hydrogen abstraction,[3b] and from organocobalt precursors[4] have been employed. A kinetic study performed by Goode and Thynne[5] produced a rate constant of $4 \times 10^5 M^{-1} s^{-1}$ at 25°C for the reaction of ethyl radicals with sulphur dioxide. This relatively high value indicated that the desired pathway (B) could compete favourably with the background decarboxylative rearrangement leading to sulphide 3[6] (path A) if sulphur dioxide is present in a large excess.

In practice, the desired transformation could be easily accomplished by using liquid sulphur dioxide as a cosolvent with dichloromethane. Thus irradiation with a tungsten lamp of a solution of the esters 1 in this mixture induced a smooth reaction affording cleanly the expected thiosulphonates 4 as white crystalline solids. The yields (not optimised) are generally good as indicated by the values in Table 1, except for cyclopropyl and t-butyl radicals which behaved poorly (entries 5 and 6) for reasons which are not yet clear.

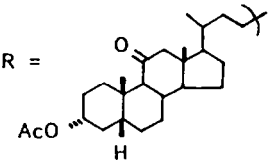
Table 1

Entry	Ester 1	Thiosulphonate 4 Yield (%)
1	1a	4a (91)
2	1b	4b (65)
3	1c	4c (90)
4	1d	4d (85)
5	1e	4e (38)
6	1f	4f (30)
7	1g	4g (54)

With a good access to the thiosulphonates in hand, we next examined briefly their synthetic utility as precursors of sulphones and sulphonamides.

Thiosulphonates are known to react with nucleophiles on the divalent sulphur with expulsion of a sulphinate[7] according to the following equation : $RSO_2SR' + Nu^{\ominus} \rightarrow RSO_2^{\ominus} + NuSR'$. Alkylation of the sulphinate would then give a sulphone. In our case, this was most simply accomplished by treating a methanolic solution of the thiosulphonate 4 with potassium hydroxide followed by addition of the alkylating agent. Sulphones 5a-5d were thus prepared in high overall yield (Table 2, entries 1-4). This route to sulphones does not involve an oxidation step; it therefore nicely complements the other alternative route through the corresponding sulphide obtained by an S_H2 reaction on a disulphide.[8]

1, 3, 4

a) R = n-$C_{15}H_{31}$-
b) R = $PhCH_2CH_2$-
c) R = cyclohexyl
d) R = 1-adamantyl
e) R = cyclopropyl
f) R = t-butyl
g) R = 

$R\text{-}SO_2R'$

5

5a R = n-$C_{15}H_{31}$-; R' = Me
5b R = cyclohexyl; R' = Me
5c R = 1-adamantyl; R' = Me
5d R = 1-adamantyl; R' = $PhCH_2$-

$RSO_2NR'R''$

6

6a R = n-$C_{15}H_{31}$-; R' = R'' = H
6b R = n-$C_{15}H_{31}$-; R' = R'' = -$(CH_2)_4$-
6c R = n-$C_{15}H_{31}$-; R' = H; R'' = cyclohexyl
6d R = n-$C_{15}H_{31}$-; R' = H; R'' = $PhCH_2$-
6e R = cyclohexyl; R' = R'' = -$(CH_2)_4$-

In parallel, access to sulphonamides 6 was secured by first converting the thiosulphonates 4 into the corresponding sulphonyl chlorides by reaction with sulphuryl chloride followed by addition of the amine. A number of sulphonamides were thus obtained in good yield (Table 2, entries 5-8).

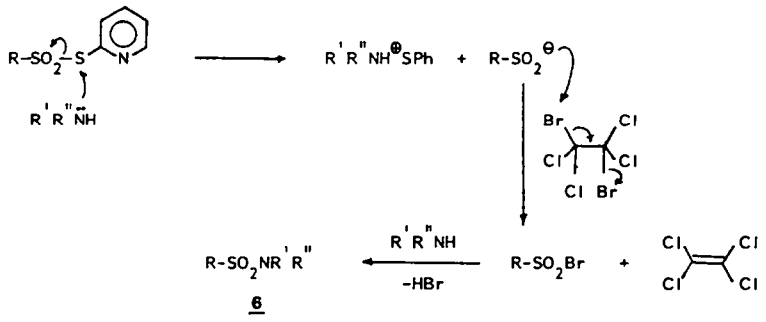
Table 2

Entry	Thiosulphonate 4	Sulphone 5 Yield (%)	Sulphonamide 6 Yield (%)
1	4a	5a (79)	-
2	4c	5b (67)	-
3	4d	5c (73)	-
4	4d	5d (89)	-
5	4a	-	6a (75)
6	4a	-	6b (93)
7	4a	-	6c (84) (45)*
8	4a	-	6d (32)*
9	4c	-	6e (60)

* Using 1,2-dibromotetrachloroethane - See text.

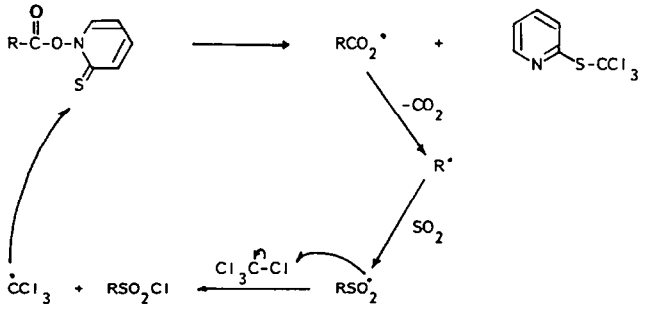
To avoid the use of the rather reactive sulphuryl chloride which would be incompatible with a sensitive starting carboxylic acid, we designed a different procedure for obtainning the sulphonamides. This involved stirring together in DMF a mixture of the thiosulphonate 4, the amine and 1,2-dibromo tetrachloroethane.[9] We conceived that the amine would cleave the

sulphur-sulphur bond in 4 to give the sulphinate which would then be oxidised by the brominating agent to the corresponding sulphonyl bromide under very mild conditions (Scheme 2). Reaction of the latter with the amine would finally give the desired sulphonamide. Preliminary experiments indicated that such a process was indeed feasible. Thus stirring 4a with an excess of 1,2-dibromo-tetrachloroethane and cyclohexylamine in DMF for 20 hours at room temperature gave the expected sulphonamide 6c in 45%. The N-benzyl analogue 6d was similarly obtained in 32% yield. Although these unoptimised yields are only modest, this approach offers the considerable advantage of very mild and essentially neutral experimental conditions, suitable for fragile substrates.



Scheme 2

We have also attempted to obtain the sulphonyl chloride directly from the thiohydroxamate ester 1 by capturing the sulphonyl radical with a chlorine atom donor such as carbon tetrachloride as outlined in Scheme 3.[10] Unfortunately, this proposition did not materialise. Replacing the dichloromethane with carbon tetrachloride did not alter the course of the reaction at least in the case of ester 1a; only the thiosulphonate 4a was formed. Clearly, the interaction of the sulphonyl radical with the starting ester is faster than chlorine abstraction from CCl_4.



Scheme 3

In summary, this modification of the original decarboxylation process has allowed a straigtforward and synthetically useful entry into a variety of thiosulphonates, sulphones, and sulphonamides. Perhaps worthy of note is that thiosulphonates themselves can have an appreciable antifungal and antimicrobial activity.[7,11]

Experimental

Melting points are uncorrected. Unless otherwise stated, NMR data (60 MHz) are for deuterochloroform solutions with tetramethylsilane as internal standard. I.R. Spectra are of Nujol mulls unless stated to the contrary. Esters 1 were prepared and used as previously described.[12] Irradiations were performed using a 250 W tungsten projector lamp cooled with a stream of air.

General Procedure for the Preparation of Thiosulphonates 4. - Dry, degassed dichloromethane (30 ml) was cooled to -40°C in a Schlenk tube under an inert atmosphere. Sulphur dioxide was then condensed into the tube until a total volums of ca. 40 ml was obtained. After warming to -10°C, ester 1 (5 mmoles) was added and the mixture stirred for a few minutes at this temperature. The cooling bath was removed and the resulting solution irradiated until the yellow colour of the ester was discharged (ca. 30 min.). The solvent was evaporated and the residue purified by chromatography on a short column of silica (CH_2Cl_2) followed by crystallisation. Yields are given in Table 1.

S-(2'-Pyridyl)-1-pentadecane Thiosulphonate 4a. - This compound crystallised from pentane-ether; m.p. 63°C; $\nu_{max.}$: 1330, 1140 cm^{-1}; δ_H: 8.47 (1H, m), 7.60 (2H, m), 7.20 (1H, m), 3.47 (2H, broad t), 0.80-1.87 (m, 29H); m/z: 321 (M^+-SO_2). Found: C, 62.29; H, 8.95; N, 3.59; S, 16.22. Calc. for $C_{20}H_{35}NO_2S_2$: C, 62.29; H, 9.15; N, 3.63; S, 16.63%.

S-(2'-Pyridyl-2-phenyl)-1-Ethane Thiosulphonate 4b. - This compound crystallised from pentane-ether; m.p. 58°C; $\nu_{max.}$: 1335, 1140 cm^{-1}; δ_H: 8.65 (1H, m), 7.33 (8H, m), 3.85 (2H, m), 3.30 (2H, m); m/z: 279 (M^+), 215 (M^+-SO_2). Found: C, 55.94; H, 4.59; N, 5.14; S, 22.68. Calc. for $C_{13}H_{13}NO_2S_2$: C, 55.89; H, 4.69; N, 5.01; S, 22.96%.

S-(2'-Pyridyl) Cyclohexane Thiosulphonate 4c. - This compound crystallised from pentane-ether; m.p. 54-55°C; $\nu_{max.}$: 1320, 1130 cm^{-1}; δ_H: 8.55 (1H, m), 7.70 (2H, m), 7.30 (1H, m), 3.50 (1H, m), 1.10 - 2.50 (10H, m); m/z: 257 (M^+), 193 (M^+-SO_2). Found: C, 51.63; H, 5.80; N, 5.35; S, 24.12. Calc. for $C_{11}H_{15}NO_2S_2$: C, 51.33; H, 5.88; N, 5.44; S, 24.92%.

S-(2'-pyridyl)-1-adamantane Thiosulphonate 4d. - This compound crystallised from pentane:ether; m.p. 74°C; $\nu_{max.}$: 1310, 1135 cm^{-1}; δ_H: 8.48 (1H, m), 7.33 (2H, m), 7.20 (1H, m), 2.08 (9H, broad s), 1.68 (6H, broad s); m/z: 245 (M^+-SO_2). Found: C, 58.52; H, 6.27; N, 4.36; S, 19.75. Calc. for $C_{15}H_{19}NO_2S_2$: C, 58.22; H, 6.19; N, 4.53; S, 20.72%.

S-(2'-pyridyl)-Cyclopropane Thiosulphonate 4e. - This compound crystallised from pentane-ether; m.p. 51-53°C; $\nu_{max.}$: 1320, 1130 cm^{-1}; δ_H (200 MHz): 9.05 (1H, d, J = 5 Hz), 8.13 (2H, m), 7.70 (1H, m), 3.25-3.43 (1H, m), 1.07-1.38 (4H, m); m/z: 215 (M^+), 187 (M^+-C_2H_4). Found: C, 44.84; H, 4.33; N, 6.35; S, 29.50. Calc. for $C_8H_9NO_2S_2$: C, 44.63; 4.21; N, 6.51; S, 29.78%.

S-(2'-pyridyl)-1,1-dimethyl-1-ethane Thiosulphonate 4f. - This compound was crystallised from pentane:ether; m.p. 88-89°C; $\nu_{max.}$: 1300, 1110 cm^{-1}; δ_H: 8.47 (1H, m), 7.73 (2H, m), 7.22 (1H, m), 1.43 (9H, s). Found: C, 47.69; H, 6.28; N, 5.80; S, 25.74. Calc. for $C_9H_{13}NO_2S_2$: C, 46.73; H, 5.66; N, 6.06; S, 27.72%.

S-(2'-pyridyl)-23-[3α-acetoxy-11-oxo-24-norcholane] Thiosulphonate 4g. - This compound was eluted with ether-dichloromethane (1:1) and crystallised also from ether:dichloromethane; m.p. 140-142°C; $[\alpha]_D$ +68° (c=1, $CHCl_3$); $\nu_{max.}$: 1730, 1700, 1300, 1110 cm^{-1}; δ_H: 8.43 (1H, m), 7.57 (2H, m), 7.23 (1H, m), 4.57 (1H, m), 3.47 (2H, m), 2.00 (3H, s); m/z: 497 (M^+-SO_2). Found: C, 64.72; H, 7.88; N, 2.72; S, 10.74. Calc. for $C_{30}H_{43}NO_5S_2$: C, 64.14; H, 7.71; N, 2.49; S, 10.42%.

General Procedure for the Preparation of Sulphones 5. - The thiosulphonate 4 (0.5 mmole) was added to a solution of KOH (1 mmole) in methanol (1.5 ml) followed by the alkylating agent (3 mmoles). The mixture was stirred at room temperature under an inert atmosphere overnight. Evaporation of the solvent and purification of the residue by preparative thin layer chromatography (CH_2Cl_2) gave the pure sulphones 5. Yields are given in Table 2.

Methyl-n-Pentadecyl Sulphone 5a. - This compound was obtained from thiosulphonate 4a and methyl iodide and crystallised from methanol; m.p.: 75°C; $\nu_{max.}$: 1140; δ_H: 3.03 (2H, broad t), 2.83 (3H, s), 0.90-1.95 (29H, m); m/z: 290 (M^+). Found: C, 65.77; H, 11.43; S, 10.89. Calc. for $C_{16}H_{34}O_2S$: C, 66.15; H, 11.80; S, 11.04.

Cyclohexyl Methyl Sulphone 5b. - This compound was obtained from thiosulphonate 4c and methyl iodide as an oil with spectral properties identical to those reported in the literature.[13]

1-Adamantyl Methyl Sulphone 5c. - This known[14] crystalline compound had a m.p. of 105°C; $\nu_{max.}$: 1140 cm^{-1}; δ_H: 2.82 (3H, s), 2.23 (3H, m), 2.13 (6H, broad s), 1.80 (6H, broad s).

1-Adamantyl Benzyl Sulphone 5d. - This compound was obtained from thiosulphonate 4d and benzyl bromide as a crystalline solid; m.p.: 176-178°C; $\nu_{max.}$: 1130 cm^{-1}; δ_H: 7.57 (5H, broad s), 3.87 (2H, broad s), 2.17 (9H, broad s), 1.73 (6H, broad s). Found: C, 70.39; H, 7.76; S, 11.27. Calc. for $C_{17}H_{22}O_2S$: C, 70.30; H, 7.64; S, 11.04%.

General Procedures for the Preparation of Sulphonamides 6. - Method A (using SO_2Cl_2).- To a solution of sulphuryl chloride (0.101 g, 0.75 mmoles) in dry dichloromethane (2 ml) was added thiosulphonate 4 (0.5 mmole) and the resulting mixture kept at room temperature for 15 hours. The requisite amine (5 mmoles) was then added and, after a further 6 hours at room temperature, the solvent was evaporated and the residue purified by preparative thin layer chromatography (dichloromethane). Yields are given in Table 2.

Method B (using $BrCl_2CCCl_2Br$).- To a solution of the thiosulphonate 4 (0.25 mmole) in DMF (1 ml) was added 1,2-dibromotetrachloro-ethane (0.651 g, 2 mmole) and the amine (2.5 mmole). The resulting mixture was kept at 60°C overnight, cooled, treated with dilluted HCl (10 ml) and extracted with ether. The organic layer was further washed with water, dried ($MgSO_4$), concentrated under reduced pressure and the residue purified by chromatography as above.

n-Pentadecane Sulphonamide 6a. - This sulphonamide was recrystallised from acetone; m.p. 100°C; $\nu_{max.}$: 3350, 3250, 1335, 1140 cm^{-1}; δ_H (acetone-d_6): 6.00 (2H, broad, exchange with D_2O), 3.08 (2H, broad t), 0.85-1.80 (29H); m/z: 291 (M^+). Found: C, 59.56; H, 11.02; N, 4.58; S, 10.90. Calc. for $C_{15}H_{31}NO_2S.^1/_2H_2O$: C, 59.96; H, 11.41; N, 4.66; S, 10.66%.

Pyrrolidyl-n-pentadecane Sulphonamide 6b. - This sulphonamide was recrystallised from methanol; m.p. 68°C; $\nu_{max.}$: 1340, 1150 cm^{-1}; δ_H: 3.28 (4H, m), 2.90 (2H, m), 0.80-2.20 (31H); m/z 345 (M^+). Found: C, 66.28; H, 11.27; N, 4.13; S, 9.20. Calc. for $C_{19}H_{39}NO_2S$: C, 66.03; H, 11.38; N, 4.05; S, 9.28%.

N-Cyclohexyl-n-pentadecane Sulphonamide 6c. - This sulphonamide was recrystallised from methanol; m.p. 76°C; $\nu_{max.}$: 3300, 1320, 1135 cm^{-1}; δ_H: 4.3 (1H, m), 3.1 (3H, m), 0.8-2.2 (39H); m/z: 373 (M^+). Found: C, 67.38; H, 11.65; N, 3.87; S, 8.57. Calc. for $C_{21}H_{43}NO_2S$: C, 67.50; H, 11.60; N, 3.75; S, 8.58%).

N-Benzyl-n-pentadecane Sulphonamide 6d. - This sulphonamide was obtained in poor yield by method B. It had a m.p. of 95°C; $\nu_{max.}$: 3250, 1320, 1140 cm^{-1}; δ_H: 7,45 (5H, broad s), 4.65 (1H, broad), 4.40 and 4.30 (2H, two broad singlets ca. 2:1 due to rotamers), 2.95 (2H, m), 0.8-2.2 (29H); m/z: 381 (M^+). Found: C, 68.53; H, 9.97; N, 3.74; S, 8.12. Calc. for $C_{22}H_{39}NO_2S$: C, 69.24; H, 10.30; N, 3.67; S, 8.40%.

Pyrrolidyl Cyclohexane Sulphonamide 6e. - This sulphonamide was isolated as an oil which slowly crystallised; m.p. 36°C; $\nu_{max.}$ (neat): 1325, 1145 cm^{-1}; δ_H: 328 (4H, broad t), 2.80 (1H, broad), 1.1-2.2 (14H, m); m/z: 217 (M^+) (no elemental analysis was secured for this compound).

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