Approaches Toward the Synthesis of 2,5-Disubstituted-1,3-thiazolidines

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Synthetic approaches for new 2,5-disubstituted-1,3-thiazolidines are described. Steric and electronic effects of the *N*-substituent of the thiazolidine ring represent the major parameter in the rearrangement process. The nmr studies demonstrate that *N*-unsubstituted 2,5-disubstituted-1,3-thiazolidines exist as epimeric mixture, while the corresponding *N*-acetylated analogues exist as a conformer mixture.

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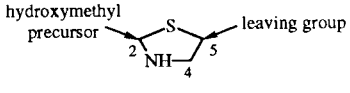
Substituted thiazolidine derivatives represent important key intermediates for the synthesis of numerous pharmacologically active drugs [1-3]. Recently a number of thiazolidines have been claimed to be retroviral protease inhibitors [2,4]. Our interest in thiazolidine derivatives stem from their possible use as a substitute for the carbohydrate moiety in the synthesis of new antiviral nucleosides. For this purpose, we have investigated the synthesis of new *N*-protected-2,5-disubstituted-1,3-thiazolidines, in which the substituent in position 5 is a leaving group and the substituent in position 2 could be easily converted into a hydroxymethyl function (Scheme 1).

Scheme 1



In order to achieve the synthesis of such intermediates, we have investigated on the one hand the direct *O*-benzoylhydroxylation of the thiazolidine using dibenzoyl peroxide [5,6] and on the other hand, the *O*-acetylhydroxylation by Pummerer reaction [7-12]. During the course of these investigations, we found that both 5-benzoylhydroxylation and 5-acetylhydroxylation reactions were under the control of electronic and steric effects induced by the *N*-substituent of the thiazolidine ring.

The synthesis of 2-benzoyloxymethyl-1,3-thiazolidine **1a** was achieved by a modification of a known procedure [13], which required the cyclization of benzoyloxyacetaldehyde [14] with 2-aminoethanethiol hydrochloride in boiling benzene. Starting from compound **1a** various *N*-substituted analogues, **1b**, **1c**, **1d** and **1e** were synthesized using different methods. The *N*-BOC compound **1b** resulted from the reaction of **1a** with di-*tert*-butyl dicarbonate in the presence of *N,N*-diisopropylethylamine (yield 93%). The *N*-trifluoroacetylthiazolidine **1c** was obtained from the condensation of compound **1a** with trifluoroacetic anhydride at room temperature in the presence of pyridine (yield 95%). The *N*-acetyl derivative **1d** was obtained from the reaction of compound **1a** with acetic anhydride in the presence of 4-dimethylaminopyridine (yield 76%). The *N*-tosyl analogue **1e** is derived from the condensation of compound **1a** and *p*-toluenesulfonyl chloride in the presence of pyridine (yield 84%).

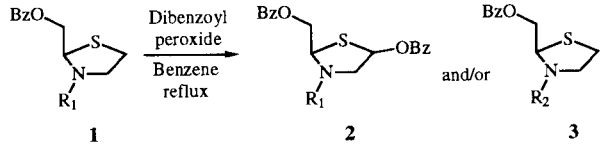
Direct Benzoylhydroxylation of Thiazolidine Using Dibenzoyl Peroxide Reagent

Compound **1a** and the corresponding *N*-substituted derivatives **1b**, **1c**, **1d** and **1e** were submitted to direct benzoylhydroxylation using dibenzoyl peroxide.

Similar reactions have been reported [5,6] in the specific case of *N*-benzoylthiazolidines carrying a carboxylic group or other related functions at the 4-position. When compounds **1a**, **1b**, **1c**, **1d** or **1e** were submitted to benzoylhydroxylation in refluxing benzene in the presence of dibenzoyl peroxide, we found that depending on the electronic and steric effects induced by the *N*-substituents, different reaction products were isolated. From the results reported in Table 1 it can be seen that the reaction did not

Table 1

Products from the Reaction of Thiazolidines with Dibenzoyl Peroxide



1 **2** **3**

Compound	R_1	Product (Yield)
1a	-H	**2a** (17%) + **3a** R_2 = OBz (15%)
1b	-C(O)O*t*Bu	no reaction
1c	$-C(O)CF_3$	no reaction
1d	$-C(O)CH_3$	**2d** (31%)
1e	$-SO_2\Phi CH_3$	**2e** (35%)

result in the expected product in both cases, *N*-BOC derivative **1b** and trifluoroacetyl analogue **1c**.

In contrast thiazolidine **1a** led in a very low yield to the desired 5-benzoyloxythiazolidine **2a** while compound **3a** was isolated as a side product. This latter compound **3a** could result from the oxidation of the secondary amine to *O*-benzoylhydroxylamine [15]. The *N*-acetyl analogue **1d** and the *N*-tosyl analogue **1e** gave the 5-benzoyloxythiazolidines **2d** and **2e** in 31 and 35% yield, respectively. In these latter cases, remaining starting material and some decomposition products were also isolated. In contrast to *N*-substituted-1,3-thiazolidine-4-carboxylic acid and related compounds, which have been reported to be isolated with clean *trans* stereochemistry due to the presence of a bulky residue in 4-position [5,6], compound **2d** was obtained as a *cis/trans* conformation mixture in a ratio of 1 to 3.

These results suggest the following comments: as far as the benzoylhydroxylation does not give the expected compound with the *N*-BOC analogue **1b**, we believe that a steric effect induced by the *tert*-butyl carbonyl group could be the prevailing parameter. This bulky group could prevent the formation of the sulphonium ylid, which is suggested to be the reactive intermediate in this electrocyclic rearrangement [16].

For compound **1c**, the use of the trifluoroacetyl group as *N*-protection group was detrimental for the reaction, similar observations were already reported by Paul *et al.* [17] in the case of 1,3-thiazolidine-4-carboxylic acid and related compounds.

Acetylhydroxylation of Thiazolidine Through the Pummerer Rearrangement

The Pummerer reaction of sulphoxides, which provides a useful method for the synthesis of α-substituted and/or α,β-unsaturated sulphides, has been widely applied in the synthesis of organosulphur compounds [7-12]. In addition, the silicon induced Pummerer rearrangement [11] was also performed by the use of several silylating reagents to functionalize thiazolidine-4-carboxylic acid or related compounds. It should be underlined that depending on the experimental conditions (catalyst type, temperature), different reaction products could result from the Pummerer rearrangement. The required sulphoxides were obtained through the usual oxidation reaction using 3-chloroperoxybenzoic acid as oxidizing agent [18]. The sulphoxides **4a**, **4b**, **4c** and **4d** were isolated and characterized as reported in the Experimental. Table 2 summarizes the results obtained by Pummerer reaction.

When the sulphoxides **4a**, **4b**, **4c** or **4d** were refluxed in acetic anhydride in the presence of sodium acetate according to the Pummerer reaction conditions [8,12], we found that depending on the structure of the *N*-protecting group, low yields of desired compounds **5a** and **5d** were obtained, while no reaction occured in the case of *N*-BOC **4b** and *N*-trifluoroacetyl **4c** sulphoxides. In each case, some starting sulphoxide was recovered while some decomposition of starting material was also observed, due to the required experimental conditions, high temperature and long reaction time. However, in contrast to reported observations [5,13,19] no ring expansion products were observed resulting from thiazolidine sulphoxide to dihydro-1,4-thiazine rearrangement, under these conditions.

NMR Studies of 2,5-Disubstituted-1,3-thiazolidines

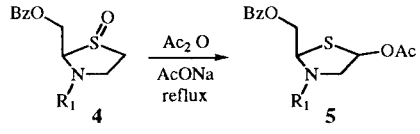
The nmr spectra of compounds **1d**, **2a**, **2d**, **5a** and **5d** present interesting properties. Indeed compounds were identified through nmr experiments (^{1}H nmr: NOEDIFF, NOESY, decoupling; ^{13}C nmr: DEPT). In the case of compound **2a**, as well as for **5a**, nmr spectra showed that each compound consists of a 1 to 1 mixture of epimers in equilibrium. The equilibration between diastereoisomers in solution is very fast on the nmr time-scale and results from epimerization at C-2 position, as suggested by the well known solution behaviour of similar thiazolidines [20-22]. A mechanism, involving a ring *seco* intermediate, probably an imine (Schiff-Base intermediate), has been suggested several times [23-25], to account for mutarotation of C-2 substituted thiazolidines (Scheme 2).

The chemical-shifts and the coupling constants assigned to protons and carbons of thiazolidine epimers for compounds **2a** and **5a** are reported in Table 3.

In the case of compounds **1d**, **2d** and **5d**, nmr spectra exhibited hindered internal rotation about the *N*-acetyl bond [19,26]. The rate of interconversion between two

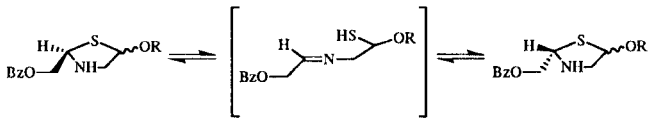
Table 2

Experimental Conditions and Products of the Pummerer Rearrangement



Sulphoxide	R_1	Reaction Time (h)	Pummerer Reaction Product (Yield)	Sulphoxide Recovered
4a	-H	12	**5a** (28%)	**4a** (15%)
4b	-C(O)O*t*Bu	72	no reaction	**4b** (85%)
4c	$-C(O)CF_3$	48	no reaction	**4c** (70%)
4d	$-C(O)CH_3$	48	**5d** (26%)	**4d** (21%)

Scheme 2



2a: R=Bz; **5a**: R=Ac

Table 3

NMR Data for Epimers **2a** and **5a** Recorded in Deuteriochloroform at 20°

	H_2 [a]	H_4	$H_{4'}$	H_5	$J_{44'}$ [b]	J_{45}	$J_{4'5}$	C-2 [a]	C-4	C-5	ratio
2a	6.07	3.95	4.30	6.46	-13.1	3.4	0	61.5	49.2	79.9	50
	5.45	3.51	5.07	6.43	-13.4	3.8	0	57.2	54.5	80.5	50
5a	5.99	3.82	4.12	6.18	-13.0	3.5	0	61.3	49.2	79.6	50
	5.40	3.39	4.85	6.15	-13.4	3.9	0	57.0	54.1	79.2	50

[a] Chemical-shift in ppm. [b] Coupling constant in Hz.

Table 4

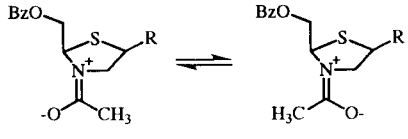
NMR Data for Compounds **2d** and **5d** Recorded in Deuteriochloroform at 20°

	CH_3	H_2 [a]	H_4	$H_{4'}$	H_5	$J_{44'}$ [b]	J_{45}	$J_{4'5}$	CH_3 [a]	C-2	C-4	C-5	ratio
trans Z	2.19	6.17	3.86	4.37	6.39	-13.3	3.1	0	22.7	58.9	54.8	80.6	60
trans E	2.21	5.55	3.43	5.26	6.29	-13.5	3.6	0	21.6	61.0	50.3	80.2	40
2d													
cis Z	2.22	5.94	4.12	4.30	6.67	-12.0	1.6	0	22.4	61.5	56.3	80.5	50
cis E	2.13	5.44	3.90	4.75	6.59	-11.4	2.2	0	21.3	62.4	53.1	79.6	50
Z	2.22	5.77	3.79	4.25	6.14	-13.2	3.4	0	22.2	60.1	55.3	80.1	50
5d													
E	2.18	5.56	3.38	5.09	6.14	-13.5	3.7	0	21.1	61.2	51.0	79.3	50

[a] Chemical-shift in ppm. [b] Coupling constant in Hz.

rotational conformers is sufficiently slow on the nmr time-scale to allow a chemical-shift difference from signals arising from the two conformers. The twin peaks arise from resonance conjugation between the p-orbital on nitrogen atom and the p-orbital of the π-electron system resulting in the two dipolar structures, *Z* and *E* forms (Scheme 3). This phenomenon was already observed in the nmr spectra of acetamido-sugar with nitrogen in the ring [10,27,28] and of *N*-acetylated thiazolidines [29].

Scheme 3



Z form *E* form

1d, R = H; **2d**, R = OBz; **5d**, R = OAc

We were able to separate the diastereoisomeric mixture of compound **2d** by column chromatography. Any NOEDIFF effect was observed between H(2) and H(5) for each diastereoisomer **2d**. However, we can propose the *cis/trans* configuration assignment of the two diastereomers based on the chemical-shifts of the C2-*C*. The ^{13}C nmr spectra show signals at 64.9 and 65.4 ppm for the *trans* **2d** compound and 66.2 and 66.5 ppm for the *cis* **2d** compound. The relative deshielding of C2-*C* in the *cis* configuration could be due to the δ-interaction of this carbon with the oxygen atom of the leaving group in 5-position [30]. The chemical-shifts and the coupling constants assigned to protons and carbons of thiazolidine in each diastereomer for compounds **2d** and **5d** are reported in Table 4. Previous workers [31-34] have shown that the carbon *syn* to the carbonyl oxygen of an amide is shielded relative to the corresponding carbon in the *anti* conformer. Thus, for each compound **2d** and **5d**, the signal corresponding to the C-4 of the two conformers at higher field, was assigned to be *syn* to the carbonyl oxygen. Likewise, the signal corresponding to the C-2 of the two conformers at lower field, was assigned to be *anti* to the carbonyl oxygen.

As far as no elimination product was obtained during *O*-benzoylhydroxylation and *O*-acetylhydroxylation reactions and no coupling constant between hydrogens H(4') and H(5) of derivatives **2a**, **2d**, **5a** or **5d** was observed, we believe that these compounds exist in a conformation where the C(5)-leaving group and C(4)-hydrogen bonds are not coplanar and can resist to a possible concerted,β-elimination process.

In conclusion, the synthesis of 2,5-disubstituted-1,3-thiazolidines has been achieved through two different methods, benzoylhydroxylation using dibenzoyl peroxide and Pummerer rearrangement. In both cases, the desired products were obtained in low yield. By its steric and electronic effects, the *N*-substituent of the thiazolidine ring plays an important role in the reaction process in both methodologies. Different nmr experiments allowed us to demonstrate that the obtained 2,5-disubstituted-1,3-thia-

zolidines exist as a mixture of two epimers in the case of *N*-unsubstituted thiazolidines **2a** and **5a** and as a mixture of two conformers in the case of *N*-acetyl-2,5-disubstituted thiazolidines **2d** and **5d**.

EXPERIMENTAL

Nuclear Magnetic Resonance spectra were recorded with a Bruker AMX-200 or AMX-400 (^{1}H nmr; ^{13}C nmr). Chemical shift values are expressed in δ values (part per million) relative to residual chloroform (7.24 ppm). Elemental analysis were determined by Service Central d'Analyse CNRS Vernaison-Lyon, France. FAB mass spectra were obtained on a JEOL DX-100 mass spectrometer (Laboratoire de Mesures Physiques-RMN, USTL, Montpellier, France) using a cesium ion source. Infrared spectra were obtained using a Perkin-Elmer 1605 FT-IR spectrophotometer, values are expressed in cm^{-1}. Melting points were determined using MEL-TEMP II, Laboratory Devices, in sealed tubes and are uncorrected. Preparative flash column chromatographies were performed using Silicagel Merck G60 230-240 mesh. Analytical thin-layer chromatographies were performed on plates silicagel $60F_{254}$ aluminium (Merck, Darmstadt) 0.2mm thickness. Benzoyloxyacetaldehyde was prepared by using known procedure [14].

2-Benzoyloxymethyl-1,3-thiazolidine (**1a**).

Benzoyloxyacetaldehyde (60.97 mmoles, 10.00 g) and 2-aminoethanethiol hydrochloride (56.77 mmoles, 6.45 g) were refluxed for 3 hours in dry benzene (200 ml) in the presence of *N,N*-diisopropylethylamine (8 ml). Water formed during the reaction was removed using a Dean-Stark apparatus. After hydrolysis with water (200 ml) and extraction with ethyl acetate (100 ml), the organic layers were washed with water (2 x 100 ml) and dried over sodium sulfate. Flash chromatography using a gradient of ethyl acetate/toluene [0% to 20%] yielded 53% (30.08 mmoles, 6.71 g) of a colorless oil which crystallized on standing, ^{1}H mnr (deuteriochloroform): δ 2.70 (m, 2H, CH_2-5), 3.31 (m, 2H, CH_2-4), 4.40 (m, 3H, C2-CH_2-O and NH, deuterium oxide-exchangeable), 4.95 (dd, 1H, CH-2), 7.38-8.08 (m, 5H, arom H). ^{13}C δ 35.3 (C-5), 51.4 (C-4), 65.9 (C-2-*C*), 68.3 (C-2), 128, 129, 133 (arom C), 166.0 (CO), ir (potassium bromide): υ NH 3300, υ CO 1718, 1270.

Anal. Calcd. for $C_{11}H_{13}NO_2S{\cdot}1.0H_2O$ (241.30): C, 54.74; H, 6.26; N, 5.80. Found: C, 55.09, H, 5.86; N, 5.42.

2-Benzoyloxymethyl-5-benzoyloxy-1,3-thiazolidine (**2a**).

Compound **1a** (8.52 mmoles, 1.90 g) dissolved in dry benzene (250 ml) was refluxed for 96 hours and dibenzoyl peroxide (12.84 mmoles, 3.11 g) was added portionwise. After evaporation of the solvent, the mixture was dissolved in dichloromethane (200 ml) and saturated sodium bicarbonate aqueous solution (150 ml) was added. The aqueous layer was extracted with dichloromethane (100 ml). Organic layers were washed twice with saturated sodium bicarbonate aqueous solution (2 x 200 ml), brine (200 ml), dried (sodium sulfate) and concentrated. Flash column chromatography using ethyl acetate/toluene [5%] yielded 17% (1.44 mmoles, 0.497 g) of an oil; ^{1}H and ^{13}C nmr show two products; ^{1}H nmr (deuteriochloroform): δ 3.51 (dd, 1H, CH_2-4), 3.95 (dd, 1H, CH_2-4), 4.30 (d, 1H, CH_2-4'), 4.38 (dd, 2H, C2-CH_2-O), 4.56 (dd, 2H, C2-CH_2-O), 5.07 (d, 1H, CH_2-4'), 5.45 (dd, 1H, CH-2), 6.07 (dd, 1H, CH-2), 6.43 (d, 1H, CH-5), 6.46 (d, 1H, CH-5), 7.39-8.39 (m, 22H, arom H and NH); ^{13}C nmr: δ 49.2 (C-4), 54.5 (C-4), 57.2 (C-2), 61.5 (C-2), 64.7 (C-2-*C*), 65.2 (C-2-*C*), 79.9 (C-5), 80.5 (C-5), 128, 129, 133 (arom C), 161.0 (CO), 161.5 (CO).

Anal. Calcd. for $C_{18}H_{19}NO_4S$: C, 62.95; H, 4.99; N, 4.08. Found: C, 63.11; H, 4.77; N, 3.95.

2-Benzoyloxymethyl-1,3-thiazolidine 1-Oxide (**4a**).

3-Chloroperoxybenzoic acid (3.17 mmoles, 0.547 g) in dichloromethane was added dropwise at 0° to a solution of thiazolidine **1a** (3.12 mmoles, 0.696 g) in dichloromethane. The reaction was stirred for 5 hours at room temperature. Then saturated sodium bicarbonate aqueous solution (50 ml) was added. The aqueous layer was extracted with dichloromethane (2 x 35 ml). Organic phases were washed with brine (100 ml), dried over magnesium sulfate and concentrated under reduced pressure. Flash chromatography using a gradient of ethyl acetate/toluene [50% to 100%] yielded 80% (2.49 mmoles, 0.597 g) of the desired sulphoxide **4a** as a yellow solid; ^{1}H and ^{13}C nmr show two products; ^{1}H nmr (deuteriochloroform): δ 1.65 (s broad, 2H, NH), 3.23 (m, 4H, CH_2-5), 3.90 (m, 1H, CH_2-4), 4.27 (m, 2H, CH_2-4'), 4.45 (m, 1H, CH_2-4), 4.53-4.93 (m, 4H, C2-CH_2-O), 5.12 (dd, 1H, CH-2), 5.42 (dd, 1H, CH-2), 7.40-8.06 (m, 10H, arom H); ^{13}C δ 41.3 (C-4), 42.9 (C-4), 49.2 (C-5), 60.5 (C-2-*C*), 61.4 (C-2-*C*), 71.3 (C-2), 72.5 (C-2), 128, 129, 133 (arom C), 161.0 (CO).

Anal. Calcd. for $C_{11}H_{13}NO_3S{\cdot}1.0H_2O$: C, 51.34; H, 5.87; N, 5.44. Found: C, 51.73; H, 5.93; N, 5.72.

2-Benzoyloxymethyl-5-acetyloxy-1,3-thiazolidine (**5a**).

Sulphoxide **4a** (2.46 mmoles, 0.588 g) and sodium acetate (1.87 mmoles, 0.255 g) were refluxed overnight in acetic anhydride. Water (30 ml) was added and aqueous layer was extracted twice with dichloromethane (2 x 35 ml). Combined organic layers were stirred for 0.5 hour with saturated sodium bicarbonate aqueous solution (50 ml). Aqueous layer was extracted with dichloromethane (20 ml), organic phase was washed with brine (20 ml) and dried over magnesium sulfate and concentrated under reduced pressure. Flash chromatography using ethyl acetate/toluene [5%] yielded 28% (0.70 mmole, 0.198 g) of an oil; ^{1}H and ^{13}C nmr show two products; ^{1}H nmr (deuteriochloroform): δ 2.05 (s, 3H, CH3), 2.06 (s, 3H, CH3), 3.39 (dd, 1H, CH_2-4), 3.82 (dd, 1H, CH_2-4), 4.12 (d, 1H, CH_2-4'), 4.29 (m, 2H, C2-CH_2O), 4.48 (m, 2H, C2-CH_2-O), 4.85 (d, 1H, CH_2-4'), 5.40 (dd, 1H, CH-2), 5.99 (dd, 1H, CH-2), 6.15 (d, 1H, CH-5), 6.18 (d, 1H, CH-5), 7.39-8.36 (m, 12H, arom H and NH); ^{13}C δ 20.8 (CH_3), 49.2 (C-4), 54.1 (C-4), 57.0 (C2), 61.3 (C-2), 64.6 (C-2-*C*), 65.2 (C-2-*C*), 79.2 (C-5), 79.6 (C-5), 128, 129, 133 (arom C), 160, 161 (NCO), 169 (*C*OCH$_3$).

Anal. Calcd. for $C_{13}H_{15}NO_4S$: C, 55.49; H, 5.37; N, 4.98. Found: C, 59.09; H, 5.27; N, 4.77.

2-Benzoyloxymethyl-3-*tert*-butoxycarbonyl-1,3-thiazolidine (**1b**).

Thiazolidine **1a** (0.21 mmoles, 0.048 g), di-*tert*-butyl dicarbonate (0.26 mmole, 0.62 ml), *N,N*-diisopropylethylamine (0.67 mmole, 117 ml) were stirred in a mixture of tetrahydrofuran/water [1:1 v/v] for 72 hours at room temperature. Tetrahydrofuran was removed under reduced pressure and crude compound was extracted with ethyl acetate (2 x 20 ml) and dried

over sodium sulfate. Evaporation of the solvent yielded 93% (0.20 mmole, 0.065 g) of a colorless oil. ^{1}H nmr (deuteriochloroform): δ 1.38 (s, 9H, *t*-Bu), 2.93-3.07 (m, 2H, CH_2-5), 3.50 (m, 2H, CH_2-4), 4.35 (m, 2H, C2-CH_2-O), 5.50 (t, 1H, CH-2), 7.39-8.07 (m, 5H, arom H).

Anal. Calcd. for $C_{16}H_{21}NO_4S$: C, 59.41; H, 6.54; N, 4.33. Found: C, 59.12; H, 6.32; N, 4.02.

2-Benzoyloxymethyl-3-*tert*-butoxycarbonyl-1,3-thiazolidine 1-Oxide (**4b**).

3-Chloroperoxybenzoic acid (0.22 mmole, 0.038 g) dissolved in dichloromethane was added dropwise at 0° to a solution of *N*-BOC-thiazolidine **1b** (0.20 mmole, 0.065 g) in dichloromethane. The reaction was stirred for 2 hours at room temperature. Then saturated sodium bicarbonate aqueous solution (30 ml) was added. Aqueous layer was extracted with dichloromethane (2 x 20 ml). Organic phases were washed with brine (60 ml), dried over sodium sulfate and concentrated. Flash chromatography using a gradient of ethyl acetate/toluene [3% to 8%] yielded 20% (0.04 mmole, 0.014 g) of the sulphoxide; ^{1}H nmr (deuteriochloroform): δ 1.40 (s, 9H, *t*-Bu), 3.52 (m, 2H, CH_2-5), 4.45 (m, 2H, CH_2-4), 4.55 (m, 2H, C2-CH_2-O), 5.52 (dd, 1H, CH-2), 7.36-8.06 (m, 5H, arom H).

Anal. Calcd. for $C_{16}H_{21}NO_5S$: C, 56.61; H, 6.23; N, 4.12. Found: C, 57.00; H, 6.32; N, 4.51.

2-Benzoyloxymethyl-3-trifluoroacetyl-1,3-thiazolidine (**1c**).

Thiazolidine **1a** (1.79 mmoles, 0.400 g), trifluoroacetic anhydride (3.58 mmoles, 0.506 ml), and pyridine (3.94 mmoles, 0.319 ml) were stirred in dichloromethane for 2 hours at room temperature. Solvents were removed; dichloromethane (10 ml) and saturated sodium bicarbonate aqueous solution (10 ml) were added. The aqueous layer was extracted with dichloromethane (10 ml). Organic phases were washed with saturated sodium bicarbonate aqueous solution (10 ml), brine (10 ml) and dried over sodium sulfate. Filtration through Celite and Silicagel pad yielded 95% (1.70 mmoles, 0.543 g) of a yellow oil; ^{1}H nmr (deuteriochloroform); δ 3.20 (m, 2H, CH_2-5), 3.90 and 4.10 (m, 2H, CH_2-4), 4.50 (d, 2H, C2-CH_2-O), 5.81 (t, 1H, CH-2), 7.41-8.02 (m, 5H, arom H); ir (potassium bromide): υ CO 1719, CF3 1448, CO 1260.

Anal. Calcd. for $C_{13}H_{12}NO_3SF_3$: C, 48.89; H, 3.79; N, 4.38. Found: C, 48.72; H, 3.28; N, 4.02.

2-Benzoyloxymethyl-3-trifluoroacetyl-1,3-thiazolidine 1-Oxide (**4c**).

3-Chloroperoxybenzoic acid (0.33 mmole, 0.057 g) in dichloromethane was added dropwise at 0° to a solution of *N*-trifluoroacetylthiazolidine **1c** (0.30 mmole, 0.097 g) in dichloromethane. The reaction was stirred for 2 hours at room temperature. Then saturated sodium bicarbonate aqueous solution (30 ml) was added. The aqueous layer was extracted with dichloromethane (2 x 20 ml). Organic layers were washed with saturated sodium bicarbonate aqueous solution (2 x 30 ml), brine (40 ml), dried over sodium sulfate and concentrated under reduced pressure. Flash chromatography using ethyl acetate/toluene [4%] yielded 65% (0.20 mmole, 0.067 g) of the sulphoxide; ^{1}H nmr (deuteriochloroform): δ 4.61-4.75 (m, 4H, CH_2-5 and C2-CH_2-O), 4.90-5.03 (m, 2H, CH_2-4), 5.53-5.60 (dd, 1H, CH-2), 7.40-8.05 (m, 5H, arom H).

Anal. Calcd. for $C_{13}H_{12}NO_4SF_3$: C, 46.56; H, 3.60; N, 4.17. Found: C, 46.18; H, 3.38; N, 3.89.

2-Benzoyloxymethyl-3-acetyl-1,3-thiazolidine (**1d**).

Compound **1a** (30.08 mmoles, 6.71 g) was refluxed for 1 hour in acetic anhydride (200 ml) containing a catalytic amount of 4-dimethylaminopyridine. After evaporation, dichloromethane (150 ml) and saturated sodium bicarbonate aqueous solution (150 ml) were added. The aqueous layer was extracted twice with dichloromethane (2 x 100 ml). Organic phases were washed with saturated sodium bicarbonate aqueous solution (3 x 150 ml), brine (200 ml), dried over sodium sulfate and concentrated. Purification by flash column chromatography using a gradient of ethyl acetate/dichloromethane [0% to 20%] yielded 76% (22.94 mmoles, 6.08 g) of a mixture of two conformers (ratio, 4:6); ^{1}H nmr (deuteriochloroform); δ 2.11 (s, 3H, CH_3), 2.18 (s, 3H, CH_3), 3.00-3.43 (m, 4H, CH_2-5), 3.72-3.90 (m, 4H, CH_2-4), 4.30-4.60 (m, 4H, C2-CH_2-O), 5.35 (dd, 1H, CH-2), 5.76 (t, 1H, CH-2), 7.39-8.00 (m, 10H, arom H); ^{13}C δ 22.9 (CH_3 *E*), 23.8 (CH_3 *Z*), 29.3 (C-5 *E*), 30.3 (C-5 *Z*), 46.0 (C-4 *E*), 49.9 (C-4 *Z*), 60.2 (C-2 *Z*), 61.8 (C-2 *E*), 65.3 (C-2-*C*), 66.5 (C-2-*C*), 128, 129, 133 (arom C), 166.0 (NCO), 168.7 (NCO); ir (potassium bromide): υ CO ester 1719, CO amide 1653, CO ester 1271.

Anal. Calcd. for $C_{13}H_{15}NO_3S$: C, 58.84; H, 5.69; N, 5.27. Found: C, 58.75; H, 6.08; N, 5.28.

2-Benzoyloxymethyl-3-acetyl-5-benzoyloxy-1,3-thiazolidine (**2d**).

Compound **1d** (22.94 mmoles, 6.08 g) dissolved in dry benzene (250 ml) was refluxed for 30 hours adding dibenzoyl peroxide (91.77 mmoles, 22.22 g) portionwise. After evaporation of the solvent, the mixture was dissolved in dichloromethane (200 ml) and saturated sodium bicarbonate aqueous solution (150 ml) was added. The aqueous layer was extracted with dichloromethane (100 ml). Organic phases were washed twice with saturated sodium bicarbonate aqueous solution (2 x 200 ml), brine (200 ml), dried (sodium sulfate) and concentrated. Flash column chromatography using a gradient of ethyl acetate/toluene [0% to 10%] yielded two compounds; *trans* isomers, 23% (5.28 mmoles, 2.036 g) of an off-white solid; ^{1}H and ^{13}C nmr show two conformers named *Z* and *E*; ^{1}H nmr (deuteriochloroform): δ 2.19 (s, 3H, CH_3 *Z*), 2.20 (s, 3H, CH_3 *E*), 3.43 (dd, 1H, CH_2-4 *E*), 3.86 (dd, 1H, CH_2-4 *Z*), 4.23-4.53 (m, 4H, C2-CH_2-O), 4.37 (d, 1H, CH_2-4' *Z*), 5.26 (d, 1H, CH_2-4' *E*), 5.55 (dd, 1H, CH-2 *E*), 6.17 (dd, 1H, CH-2 *Z*), 6.29 (d, 1H, CH_2-5 *E*), 6.39 (d, 1H, CH_2-5 *Z*), 7.34-8.08 (m, 20H, arom H); ^{13}C δ 21.6 (CH_3 *E*), 22.7 (CH_3 *Z*), 50.3 (C-4 *E*), 54.8 (C-4 *Z*), 58.9 (C-2 *Z*), 61.0 (C-2 *E*), 64.9 (C-2-*C*), 65.4 (C-2-*C*), 80.2 (C–5 *E*), 80.6 (C-5 *Z*), 128, 129, 133 (arom C), 165.7 (CO), 169.2 (CO); ms: (FAB>0, matrix, glycerol-thioglycerol, 1:1, v/v) m/z 386 $[M + H]^+$; ir (potassium bromide): υ CO ester 1719, CO amide 1664, CO ester 1264.

Anal. Calcd. for $C_{20}H_{19}NO_5S$: C, 62.32; H, 4.96; N, 3.63. Found: C, 61.99; H, 5.12; N, 3.54.

The cis isomers obtained in 8% yield (1.76 mmoles, 0.681 g) as a foam; ^{1}H and ^{13}C nmr show two conformers named *Z* and *E*; ^{1}H nmr (deuteriochloroform); δ 2.13 (s, 3H, CH_3 *E*), 2.22 (s, 3H, CH_3 *Z*), 3.90 (dd, 1H, CH_2-4 *E*), 4.12 (dd, 1H, CH_2-4 *Z*), 4.40 and 4.80 (m, 4H, C2-CH_2-O), 4.30 (d, 1H, CH_2-4', *Z*), 4.75 (d, 1H, CH_2-4' *E*), 5.44 (dd, 1H, CH-2 *E*), 5.94 (t, 1H, CH-2 *Z*), 6.59 (dd, 1H, CH_2-5 *E*), 6.67 (dd, 1H, CH_2-5 *Z*), 7.33-8.14 (m, 20H, arom H); ^{13}C δ 21.3 (CH_3 *E*), 22.4 (CH_3 *Z*), 53.1 (C-4 *E*), 56.3 (C-4 *Z*), 61.5 (C-2 *Z*), 62.4 (C-2 *E*), 66.2 (C-2-*C*), 66.5 (C-2-*C*), 79.6 (C-5 *E*), 80.5 (C-5 *Z*), 128, 129, 130, 133 (arom C),

166.0 (NCO), 168.8 (NCO), 170.8 (CO); ms: (FAB>0, matrix, glycerol-thioglycerol, 1:1, v/v) m/z 386 $[M + H]^+$; ir (potassium bromide): υ CO ester 1720, CO amide 1662, CO ester 1267.

Anal. Calcd. for $C_{20}H_{19}NO_5S$: C, 62.32; H, 4.96; N, 3.63. Found: C, 62.11; H, 5.29; N, 3.26.

2-Benzoyloxymethyl-3-acetyl-1,3-thiazolidine 1-Oxide (**4d**).

3-Chloroperoxybenzoic acid (3.17 mmoles, 0.547 g) dissolved in dichloromethane was added dropwise at 0° to a solution of *N*-acetyl thiazolidine **1d** (3.12 mmoles, 0.696 g) in dichloromethane (100 ml). The reaction was stirred for 3 hours at room temperature. Then saturated sodium bicarbonate aqueous solution (50 ml) was added. The aqueous layer was extracted with dichloromethane (2 x 50 ml). Organic layers were washed with brine (100 ml), dried (sodium sulfate) and concentrated. Flash chromatography using a gradient of ethyl acetate/hexane [75% to 100%] yielded 80% (2.49 mmoles, 0.597 g) of the desired sulphoxide; ^1H nmr shows two conformers; ^1H nmr (deuteriochloroform): δ 2.21 (s, 3H, CH_3), 2.26 (s, 3H, CH_3), 3.08-3.38 (m, 4H, CH_2-5), 4.07-4.16 (m, 2H, CH_2-4), 4.28-4.39 (m, 2H, CH_2-4), 4.42-4.62 (m, 4H, C2-CH_2-O), 5.20 (dt, 1H, CH-2), 5.49 (dt, 1H, CH-2), 7.41-8.03 (m, 10H, arom H).

Anal. Calcd. for $C_{13}H_{15}NO_4S$: C, 54.49; H, 5.37; N, 4.98. Found C, 54.53; H, 5.64; N, 4.92.

2-Benzoyloxymethyl-3-acetyl-5-acetyloxy-1,3-thiazolidine (**5d**).

Sulphoxide **4d** (0.83 mmole, 0.234 g) and sodium acetate (0.81 mmole, 0.067 g) were refluxed for 48 hours in acetic anhydride. Water (30 ml) was added and the aqueous layer was extracted twice with dichloromethane (2 x 35 ml). Organic layers were stirred for 0.5 hour with saturated sodium bicarbonate aqueous solution (50 ml), then washed with brine (20 ml), dried over magnesium sulfate and concentrated under reduced pressure. Flash chromatography using a gradient of ethyl acetate/toluene [0% to 10%] yielded 26% (0.21 mmole, 0.071 g) of an oil; ^1H nmr shows two conformers; ^1H nmr (deuteriochloroform): δ 2.04 (s, 3H, CH_3), 2.06 (s, 3H, CH_3), 2.18 (s, 3H, CH_3 *E*), 2.22 (s, 3H, CH_3 *Z*), 3.38 (dd, 1H, CH_2-4 *E*), 3.79 (dd, 1H, CH_2-4 *Z*), 4.25 (d, 1H, CH_2-4' *Z*), 4.28-4.38 (m, 2H, C2-CH_2-O), 4.42-4.56 (m, 2H, C2-CH_2-O), 5.09 (d, 1H, CH_2-4' *E*), 5.56 (dd, 1H, CH-2 *E*), 5.77 (t, 1H, CH-2 *Z*), 6.14 (m, 2H, CH-5), 7.38-8.11 (m, 10H, arom H); ^{13}C nmr δ 21.1 (CH_3 *E*), 22.2 (CH_3 *Z*), 51.0 (C-4 *E*), 55.3 (C-4 *Z*), 60.1 (C-2 *Z*), 61.2 (C-2 *E*), 64.2 (C-2-*C*), 64.5 (C-2-*C*), 79.3 (C-5 *E*), 80.1 (C-5 *Z*), 128, 129, 133 (arom C), 160.0 (CO), 161.8 (CO), 167.0 (*C*OCH_3).

Anal. Calcd. for $C_{15}H_{17}NO_5S$: C, 55.71; H, 5.30; N, 4.33. Found: C, 55.98; H, 5.21; N, 4.66.

2-Benzoyloxymethyl-3-tosyl-1,3-thiazolidine (**1e**).

Thiazolidine **1a** (1.33 mmoles, 0.298 g), *p*-toluenesulfonyl chloride (2.71 mmoles, 0.517 g), and pyridine (2.95 mmoles, 0.240 ml) were stirred in dichloromethane overnight at room temperature. Water (25 ml) was added; the organic layer was washed with saturated sodium bicarbonate aqueous solution (2 x 30 ml), brine (40 ml), dried over sodium sulfate and concentrated to dryness. Flash chromatography using a gradient of ethyl acetate/toluene [1% to 8%] yielded 84% (1.12 mmoles, 0.425 g) of *N*-tosyl thiazolidine **1e** as a white solid. mp 116-117°; ^1H nmr (deuteriochloroform); δ 2.39 (s, 3H, CH_3), 2.48 and 2.90 (m, 2H, CH_2-5), 3.53 and 4.07 (m, 2H, CH_2-4), 4.34 (m, 2H, C2-CH_2-O), 5.48 (dd, 1H, CH2), 7.23-8.08 (m, 9H, arom H); ir (potassium bromide): υ CO ester 1718, SO_2 1351, CO ester 1273, SO_2 1163.

Anal. Calcd. for $C_{18}H_{19}NO_4S_2$: C, 57.27; H, 5.07; N, 3.71. Found: C, 57.06; H, 4.95; N, 3.38.

2-Benzoyloxymethyl-3-tosyl-5-benzoyloxy-1,3-thiazolidine (**2e**).

N-Tosylthiazolidine **1e** (0.45 mmole, 0.171 g) dissolved in dry benzene (20 ml) was refluxed for 90 hours and dibenzoyl peroxide (0.50 mmole, 0. 121 g) was added portionwise. After evaporation of the solvent, the mixture was dissolved in dichloromethane (25 ml) and saturated sodium bicarbonate aqueous solution (25 ml) was added. The aqueous layer was extracted with dichloromethane (15 ml). Organic phases were washed twice with saturated sodium bicarbonate aqueous solution (2 x 25 ml), brine (25 ml), dried over sodium sulfate and concentrated. Flash column chromatography using toluene yielded 35% (0.16 mmole, 0.079 g) of an oil; ^1H nmr (deuteriochloroform): δ 2.43 (s, 3H, CH_3), 4.06 (dd, 1H, CH_2-4), 4.30-4.46 (m, 2H, C2-CH_2-O), 4.75 (dd, 1H, CH_2-4',), 5.55 (dd, 1H, CH-2), 6.33 (dd, 1H, CH-5), 7.27-8.14 (m, 14H, arom H).

Anal. Calcd. for $C_{25}H_{23}NO_6S$: C, 60.34; H, 4.65; N, 2.81. Found: C, 59.96; H, 4.35; N, 3.02.

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