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Synthesis of Benzo[d]-1,2-thiazole-1,1-dioxide Derivatives *via* Directed Lithiation of 2,2-Dimethyl-N-(phenylsulfonyl)-propanamides

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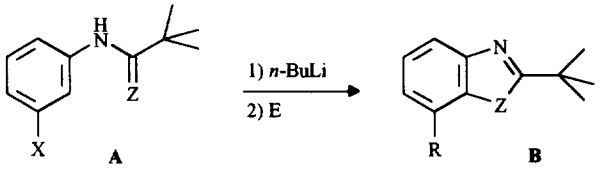
Abstract: A novel synthesis of 7-substituted benzo[d]-1,2-thiazole-1,1-dioxides **4** is presented including directed lithiation of 2,2-dimethyl-N-(phenylsulfonyl)-propanamides **1 - 3** , aryne-mediated cyclization and subsequent quenching of aryllithium intermediates with various electrophiles. A proposed mechanism is rationalized by some control experiments. © 1997 Elsevier Science Ltd. All rights reserved.

INTRODUCTION

In the 1960´s, Huisgen[1] described first examples of benzyne-mediated cyclization reactions for the synthesis of some indole and quinoline derivatives. Although intramolecular trapping of aryne intermediates by an adjacent side chain bearing a nucleophilic center offers a very general synthetic methodology for the build-up of heterocyclic ring systems, only few applications appeared in the literature in the following two decades.[2] In 1982 Clark and Caroon[3] picked up the idea again developing a synthesis of benzoxazoles and providing a useful extension by application of various functional electrophiles. Thus, arynes were generated *via* directed lithiation of N-pivaloyl-3-fluoroaniline (**A**, Z=O) with *n*-BuLi and immediately trapped by cyclization to form aryllithium intermediates which led to 7-substituted 2-*t*-butylbenzoxazoles (**B**, Z=O) upon quenching with suitable electrophiles. Recently, we have shown that

this approach can also be applied successfully to the synthesis of related benzothiazoles (**B**, Z=S) when starting with corresponding thioamides (**A**, Z = S)[4] (Scheme 1).



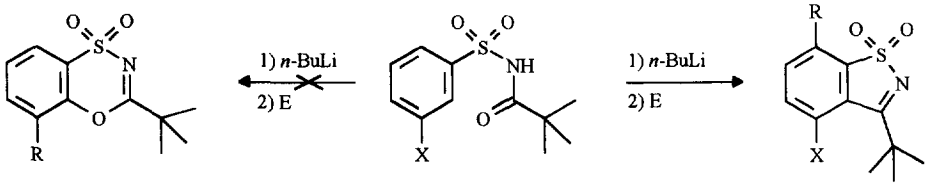
X = F, Cl Z = O, S R = CHO, COOH, CONHtBu, COPh

Scheme 1

In order to further exploit this methodology we started to modify the side chains aiming towards the synthesis of some 6-membered heterocyclic ring systems. One of these attempts led us to the N-arylsulfonyl-carboxamide moiety which seemed to fit the requirements of this reaction sequence. Although the use of sulfonamides as *ortho*-directing groups is well documented in the literature,[5] we are aware of only two papers where N-arylsulfonyl-carboxamides were used in this context. Abramovitch et al.[6] reported the lithiation of *para*-substituted N-phenylsulfonyl-carboxamides leading to 2-alkyl- and 2-aryl-benzisothiazole-1,1-dioxides in disappointing 2-9% yield, whereas Wolfe et al.[7] succeeded more recently in analogous cyclizations of various, mainly N-(2-chlorophenylsulfonyl)-carboxamides with LDA. In both papers only H_2O was used as the electrophile in the course of the work-up procedure.

RESULTS AND DISCUSSION

Following our intention to use the sequence -- 1. lithiation, 2. aryne mediated cyclization, 3. quenching of the aryllithium with electrophiles -- for the synthesis of 6-membered heterocyclic systems we started with an attempt to build up the 1,4,3-benzoxathiazine system (**C**) by lithiation of N-(3-fluorophenylsulfonyl)-2,2-dimethylpropanamide **2**. The pivaloyl group with its sterically hindered carbonyl group was chosen to prevent the direct attack of the aryllithium compound generated in the initial directed lithiation step. This choice should lead to the formation of the desired aryne followed by subsequent cyclization to **C**. A series of experiments (with X = F and Cl) dashed down our expectations as we were not able to find suitable reaction conditions to prevent the undesired ring closure to the benzisothiazole system. On the other hand careful analysis of the reaction mixtures obtained by lithiation and subsequent quenching of the intermediates with functional electrophiles led to a surprising discovery. Beside of the product of the simple cyclization we also isolated substituted benzisothiazoles of the general formula **4**, showing a substitution pattern not easily accessible by routine synthetic methods (Scheme 2). By optimization of the reaction parameters we are now able to present a general procedure for the synthesis of these products making them available in synthetically useful yields.



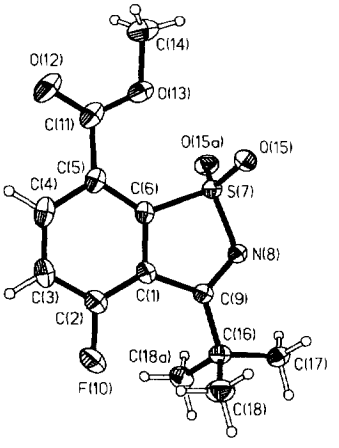
C

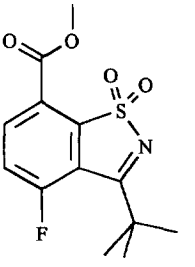
1: X = H; **2**: X = F; **3**: X = Cl

4

Scheme 2

The structure of the isolated products **4** was initially assigned by NMR analysis of the H-F- and C-F-couplings of the fluorosubstituted carboxylic acid **4g**. Appearence of a $^{3}J_{HF}$-coupling of 10 Hz as well as a $^{2}J_{CF}$-coupling of 28 Hz at the definitely unsubstituted 5-position referred to the 7-substituted product. Additionally, a product bearing the carboxyl group at 5-position would show the CO-signal splitted by a $^{3}J_{CF}$-coupling of approximately 10 Hz which was not observed in the ^{13}C NMR of the isolated product. The result of the NMR analysis was later confirmed by X-ray diffraction on the methylester **5** as shown in the ORTEP diagram in Figure 1.[8]





5

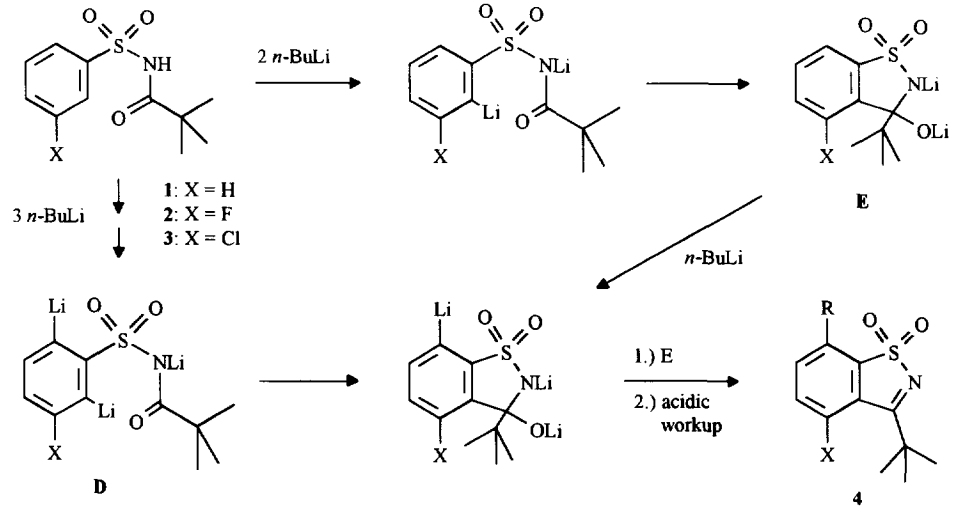
Figure 1. Crystal structure of the methylester **5** (ORTEP plot, 30% ellipsoids).

The results of a series of experiments undertaken to check the scope and limitations of this protocol are summarized in the following table.

Table: Benzo[d]-1,2-thiazole-1,1-dioxides **4** *via* Directed Lithiation of N-(Phenylsulfonyl)-carboxamides (**1**, **2** and **3**) Followed by Cyclization and Trapping with Electrophiles in 7-Position

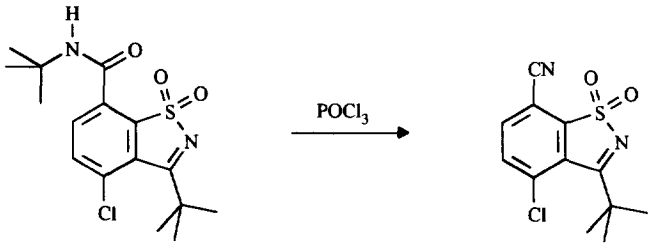
entry	starting material	E	product	X	R	yield[%]
1	**1**	H_2O	**4a**	H	H	74
2	**1**	DMF	**4b**	H	CHO	43
3	**1**	*t*-BuNCO	**4c**	H	CONH*t*-Bu	39
4	**1**	CO_2	**4d**	H	COOH	23
5	**2**	H_2O	**4e**	F	H	67
6	**2**	*t*-BuNCO	**4f**	F	CONH*t*-Bu	64
7	**2**	CO_2	**4g**	F	COOH	55
8	**3**	H_2O	**6**	Cl	H	72
9	**3**	*t*-BuNCO	**4i**	Cl	CONH*t*-Bu	59
10	**3**	PhCHO	**4j**	Cl	CH(OH)Ph	39
11	**3**	MeI	**4k**	Cl	CH_3	60
12	**3**	CO_2	**4l**	Cl	COOH	49
13	**3**	$B(OMe)_3$ / H_2O_2	**4m**	Cl	OH	46

The observed substitution in 7-position can be rationalized by the assumption that a N,2,6-trilithiated intermediate (**D**) occurs before cyclization or - more probably - by subsequent lithiation of the cyclized intermediate (**E**). As there are only very few examples reported in the literature[9] where dilithiation has been achieved the two-step mechanism was favoured. All possible intermediates in the course of the proposed synthetic sequence are shown in Scheme 3.



Scheme 3

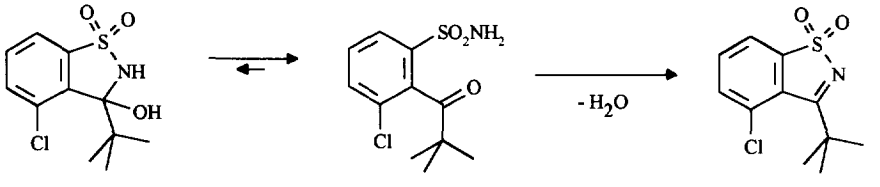
Entries 1 to 4 show that although the halogen in 3-position is not necessary for lithiation and cyclization the yields of the 7-substituted halogen-free products **4b-d** are considerably lower, clearly indicating that the second lithiation step is facilitated by the halogen in 4-position. The nitrile **4n** was obtained by reaction of the N-*t*-butylcarboxamide **4i** with $POCl_3$.



4i **4n**

Scheme 4

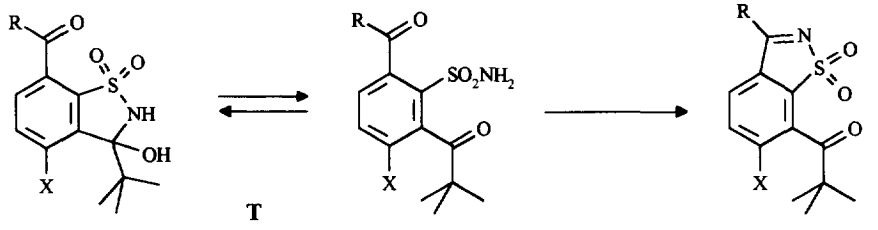
In contrast to the synthesis of **4a** and **4e** not the expected 4-chloroproduct **4h** was isolated when starting the reaction sequence with **3** and adding water as the electrophile but surprisingly 3-chloro-2-(2,2-dimethyl-1-oxopropyl)-benzenesulfonamide as the more stable ring-chain tautomer of **6**. The cyclization to the desired benzo[d]-1,2-thiazole derivative **4h** was achieved by thermal dehydration of **6** at 170°C (Scheme 5).



6 **4h**

Scheme 5

When the intermediates obtained from the lithiation of **2** and **3** were quenched with DMF or benzonitrile unexpected products (**7a-c**) were isolated formed by an alternative cyclization of the ring-opened ring-chain tautomer **T** with the introduced, more reactive formyl or benzoyl group (Scheme 6). It is interesting to note that this cyclization did not occur when the reaction sequence was started with the halogen free educt **1**. The aldehyde **4b** once isolated is stable under the work-up conditions and does not yield the corresponding ring-opening-ring-closure product similar to **7a** and **7b**.

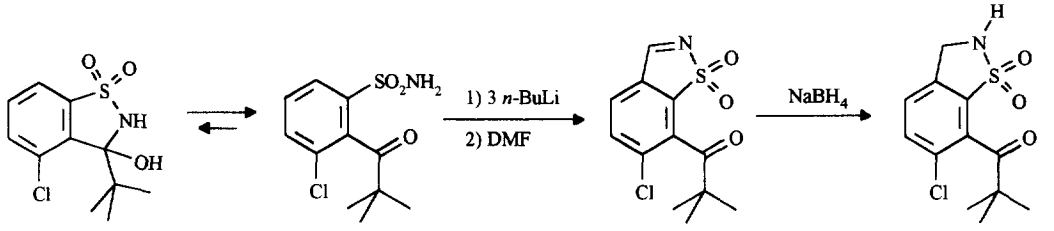


T

7a: X=F, R=H ; **7b**: X=Cl, R=H
7c: X=Cl, R=Ph

Scheme 6

In a control experiment depicted in Scheme 7 the lithiation of **6** was performed under standard conditions and upon quenching with DMF the known product **7b** was isolated in comparable yield assigning a higher probability to the postulated lithiation-cyclization-lithiation mechanism *via* the intermediate **E** illustrated in Scheme 3. Reduction of **7b** by $NaBH_4$ led to the sultam **8**.



6 **7b** **8**

Scheme 7

The halogenated N-(phenylsulfonyl)-carboxamides **2** and **3** were obtained by diazotization of 3-fluoroaniline and 3-chloroaniline, respectively, followed by treatment with a $NaHSO_3$ solution under Sandmeyer conditions. The obtained sulfonyl chlorides were then converted into the corresponding sulfonamides with conc. ammonia followed by acylation with pivaloyl chloride in pyridine. **1** was prepared likewise from commercially available benzenesulfonamide.

EXPERIMENTAL SECTION

Starting materials: 3-Fluorophenylsulfonyl chloride (bp. 125°C/19 mbar; ref.[10] 112-113°C/12 Torr), 3-chlorophenylsulfonyl chloride (bp. 128-131°C/10 mbar; ref.[11a] 134°C/12 Torr; ref.[11b] 85-89°C/1 Torr), 3-fluorophenylsulfonamide (mp. 129-131°C; ref.[12] 124°C, ref.[10] 129-130°C) and 3-chlorophenylsulfonamide (mp. 148-149°C; ref.[13a,b] 148°C, ref.[13c] 147°C) were prepared according to the literature[11a,14].

2,2-Dimethyl-N-(phenylsulfonyl)-propanamides 1, 2 and 3. General procedure.

A solution of the corresponding benzenesulfonamide (0.1 mol) in dry pyridine (100 ml) was treated carefully with pivaloylchloride (0.2 mol). After stirring at room temperature for 48 h the reaction mixture was poured in cold 2n HCl (1000 ml) and extracted with ethyl acetate (1500 ml). The combined organic layers were reextracted with 2n HCl (150 ml) to remove all pyridine, dried over Na_2SO_4, the solvent evaporated and the residue recrystallized from diisopropyl ether.

2,2-Dimethyl-N-(phenylsulfonyl)-propanamide (1)

Yield: 85%, colourless crystals, mp 124-125°C. ^{1}H NMR ($CDCl_3$): δ = 1.18 (s, 9H, $C(CH_3)_3$), 7.5-7.7 (m, 3H, H-3, H-4, H-5), 8.08 (d, 2H, H-2, H-6, $J_{23,65}$ = 7.5 Hz), 8.45 (bs, 1H, NH); ^{13}C NMR ($CDCl_3$): δ = 26.6 (q, $C(\underline{C}H_3)_3$), 40.0 (s, $\underline{C}(CH_3)_3$), 128.3 (d, C-2, C-6), 128.9 (d, C-3, C-5), 133.9 (d, C-4), 138.4 (s, C-1), 176.0 (s, CO). Anal. Calcd. for $C_{11}H_{15}NO_3S$ (241.31) C 54.75; H 6.27; N 5.80. Found C 54.53; H 6.32; N 5.92.

2,2-Dimethyl-N-[(3-fluorophenyl)sulfonyl]-propanamide (2)

Yield: 93%, colourless crystals, mp 118-120°C. ^{1}H NMR ($CDCl_3$) : δ = 1.15 (s, 9H, $C(C\underline{H}_3)_3$), 7.27-7.40 (m, 1H, H-4), 7.48-7.61 (m, 1H, H-5), 7.69-7.81 (m, 1H, H-2), 7.81-7.91 (m, 1H, H-6); ^{13}C NMR ($CDCl_3$) : δ = 26.5 (q, $C(\underline{C}H_3)_3$), 40.0 (s, $\underline{C}(CH_3)_3$), 115.7 (dd, $^2J_{CF}$ = 21 Hz, C-2), 121.2 (dd, $^2J_{CF}$ = 25 Hz, C-4), 124.0 (dd, $^4J_{CF}$ = 3 Hz, C-6), 130.8 (dd, $^3J_{CF}$ = 8 Hz, C5), 140.3 (ds, $^3J_{CF}$ = 7 Hz, C-1), 162.0 (ds, $^1J_{CF}$ = 250 Hz, C-3), 176.2 (s, CO). Anal. Calcd. for $C_{11}H_{14}FNO_3S$ (259.30) C 50.95; H 5.44; N 5.40. Found C 51.01; H 5.35; N 5.37.

N-[(3-Chlorophenyl)sulfonyl]-2,2-dimethylpropanamide (3)

Yield: 82%, colourless crystals, mp 149-152°C. ^{1}H NMR ($CDCl_3$): δ = 1.2 (s, 9H, $C(CH_3)_3$), 7.50 (t, 1H, H-5, $J_{54,56}$ = 8 Hz), 7.61 (d, 1H, H-4, J_{45} = 8 Hz), 7.98 (d, 1H, H-6, J_{65} = 8 Hz), 8.04 (s, 1H, H-2), 8.8 (bs, 1H, NH); ^{13}C NMR ($CDCl_3$): δ = 26.6 (q, $C(\underline{C}H_3)_3$), 40.1 (s, $\underline{C}(CH_3)_3$), 126.5 (d, C-6), 128.3 (d, C-2), 130.3 (d, C-5), 134.1 (d, C-4), 135.1 (s, C-3), 140.0 (s, C-1), 176.1 (s, CO). Anal. Calcd. for $C_{11}H_{14}ClNO_3S$ (275.76) C 47.91; H 5.12; N 5.08. Found C 48.12; H 4.95; N 4.94.

Synthesis of benzo[d]-1,2-thiazole-1,1-dioxide derivatives 4 and 7 *via* directed lithiation of N-phenylsulfonylcarboxamides. General procedure.

n-BuLi (2.5M solution in hexane, 3.5eq.) was added at -80°C to a 5% solution of N-(phenylsulfonyl)-carboxamide **1-3** (1eq.) in THF. After gradual warming to -10°C the mixture was cooled again and the electrophile (1.5eq.) added at -75°C, the reaction mixture stirred for 8 h, hydrolyzed with H_2O or 2N HCl and extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4, filtered and evaporated *in vacuo*. The crude products were usually purified by flash chromatography.

3-(1,1-Dimethylethyl)-benzo[d]-1,2-thiazole-1,1-dioxide (4a)

Yield: 74%, colourless crystals, mp 126-128°C (ref.[15]: 128-130°C). ^{1}H NMR ($CDCl_3$): δ = 1.51 (s, 9H, $C(CH_3)_3$), 7.69-7.87 (m, 2H, H-6, H-5), 7.87-8.00 (m, 2H, H-4, H-7); ^{13}C NMR ($CDCl_3$): δ = 28.1 (q, $C(\underline{C}H_3)_3$), 38.4 (s, $\underline{C}(CH_3)_3$), 122.4 (d, C-7), 126.6 (d, C-4), 129.5 (s, C-3a), 132.8 (d, C-6), 133.5 (d, C-5), 140.7 (s, C-7a), 181.5 (s, C-3). Anal. Calcd. for $C_{11}H_{13}NO_2S$ (223.30) C 59.17; H 5.87; N 6.27. Found C 58.98; H 5.84; N 6.20.

3-(1,1-Dimethylethyl)-benzo[d]-1,2-thiazole-1,1-dioxide-7-carboxaldehyde (4b)

Yield: 43%, colourless crystals, mp 196-200°. ^{1}H NMR ($CDCl_3$): δ = 1.56 (s, 9H, $C(CH_3)_3$), 7.90 (t, 1H, H-5, J = 7.3 Hz), 8.18 (d, 2H, H-4, H-6, J = 7.3 Hz), 10.48 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$): δ = 28.2 (q, $C(\underline{C}H_3)_3$), 38.5 (s, $\underline{C}(CH_3)_3$), 130.98 (s, C-3a*), 131.03 (d, C-6), 132.0 (s, C-7*), 132.2 (d, C-5), 134.3 (d, C-4), 141.8 (s, C-7a), 180.3 (s, C-3), 186.3 (d, CHO). Anal. Calcd. for $C_{12}H_{13}NO_3S$ (251.31) C 57.35; H 5.21; N 5.57. Found C 57.09; H 5.24; N 5.45.

3-(1,1-Dimethylethyl)-N-(1,1-dimethylethyl)-benzo[d]-1,2-thiazole-1,1-dioxide-7-carboxamide (4c)

Yield: 39%, colourless crystals, mp 166-170°C. ^{1}H NMR ($CDCl_3$): δ = 1.51 (s, 9H, $C(CH_3)_3$*), 1.53 (s, 9H, $NC(CH_3)_3$*), 7.18 (bs, 1H, NH), 7.76 (t, 1H, H-5, J = 7.6 Hz), 8.01 (d, 1H, H-4, J = 7.6 Hz), 8.17 (d, 1H, H-6, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$): δ = 28.2 (q, $C(\underline{C}H_3)_3$*), 28.3 (q, $NC(\underline{C}H_3)_3$*), 38.4 (s, $\underline{C}(CH_3)_3$), 52.7 (s, $N\underline{C}(CH_3)_3$), 128.4 (s, C-7*), 128.5 (d, C-4*), 129.6 (s, C-3a), 133.7 (d, C-6*), 134.0 (d, C-5*), 137.7 (s, C-7a), 162.4 (s, CONH), 181.5 (s, C-3). Anal. Calcd. for $C_{16}H_{22}N_2O_3S$ (322.43) C 59.60; H 6.88; N 8.69. Found C 59.30; H 6.86; N 8.46.

3-(1,1-Dimethylethyl)-benzo[d]-1,2-thiazole-1,1-dioxide-7-carboxylic acid (4d)

Yield: 23%, colourless crystals, mp 282-292°C (decomp.). ^{1}H NMR (DMSO-d6): δ = 1.48 (s, 9H, $C(CH_3)_3$), 7.98 (t, 1H, H-5, $J_{45,56}$ = 6.0 Hz), 8.28 (d, 1H, H-4, J_{45} = 6.0 Hz), 8.50 (d, 1H, H-6, J_{56} = 6.0 Hz); ^{13}C NMR (DMSO-d6): δ = 27.7 (q, $C(\underline{C}H_3)_3$), 37.7 (s, $\underline{C}(CH_3)_3$), 128.0 (s, C-7), 130.1 (s, C-3a), 131.3 (d, C-4), 134.1 (d, C-6), 135.2 (d, C-5), 140.1 (s, C-7a), 163.6 (s, COOH), 178.9 (s, C-3). Anal. Calcd. for $C_{12}H_{13}NO_4S$ (267.30) C 53.92; H 4.90; N 5.24. Found C 53.94; H 4.79; N 5.16.

3-(1,1-Dimethylethyl)-4-fluoro-benzo[d]-1,2-thiazole-1,1-dioxide (4e)

Yield: 67%, colourless crystals, mp 130-134°C. ^{1}H NMR ($CDCl_3$): δ = 1.47 (s, 9H, $C(CH_3)_3$), 7.4-7.5 (m, 1H, H-5), 7.75-7.85 (m, 2H, H-6, H-7); ^{13}C NMR ($CDCl_3$): δ = 26.5 (q, $C(\underline{C}H_3)_3$), 38.0 (s, $\underline{C}(CH_3)_3$), 117.1 (s, $^2J_{CF}$ = 19 Hz, C-3a), 119.0 (d, C-7), 122.5 (d, $^2J_{CF}$ = 28 Hz, C-5), 136.1 (d, $^3J_{CF}$ = 6 Hz, C-6), 143.1 (s, $^3J_{CF}$ = 3 Hz, C-7a), 155.9 (s, $^1J_{CF}$ = 262 Hz, C-4), 179.2 (s, C-3).

3-(1,1-Dimethylethyl)-N-(1,1-dimethylethyl)-4-fluoro-benzo[d]-1,2-thiazole-1,1-dioxide-7-carboxamide (4f)

Yield: 64%, colourless crystals, mp 157-159°C. ^{1}H NMR ($CDCl_3$) : δ = 1.31 (s, 9H, $C(C\underline{H}_3)_3$), 1.53 (s, 9H, $C(C\underline{H}_3)_3$), 7.15 (bs, 1H, NH), 7.48 (dd, $^2J_{HF}$ =7 Hz, J_{56} = 9 Hz, 1H, H-5), 8.20 (dd, $^3J_{HF}$ = 4 Hz, J_{65}= 8 Hz, 1H, H-6); ^{13}C NMR ($CDCl_3$) : δ = 26.6 (q, $C(\underline{C}H_3)_3$), 28.3 (q, $NHC(\underline{C}H_3)_3$), 38.4 (s, $NH\underline{C}(CH_3)_3$), 53.0 (s, $\underline{C}(CH_3)_3$), 119.6 (ds, $^2J_{CF}$ = 22 Hz, C-3a), 123.1 (dd, $^2J_{CF}$ = 28 Hz, C-5), 130.7 (ds, $^3J_{CF}$ = 3 Hz, H-7a*), 137.9 (dd, $^3J_{CF}$ = 9 Hz, C-6), 140.0 (s, C-7*), 157.2 (ds, $^1J_{CF}$ = 270 Hz, C-4), 161.6 (s, $NH\underline{C}O$), 179.5 (ds, $^3J_{CF}$ = 2 Hz, C-3). Anal. Calcd. for $C_{16}H_{21}FN_2O_3S$ (340.41) C 56.45; H 6.22; N 8.23. Found C 56.72; H 6.16; N 8.02.

4-Fluoro-3-(1,1-dimethylethyl)-benzo[d]-1,2-thiazole-1,1-dioxide-7-carboxylic acid (4g)

Yield: 55 %, light yellow crystals, mp 230-241°C (decomp.). ^{1}H NMR (DMSO-d_6) : δ = 1.36 (s, 9H, $C(C\underline{H}_3)_3$), 7.89 (dd, J_{56} = 9 Hz, $^3J_{HF}$ = 11 Hz, 1H, H-5), 8.38 (dd, J_{65} = 9 Hz, $^4J_{HF}$ = 4 Hz, 1H, H-6), 14.50 (bs, 1H, OH); ^{13}C-NMR (DMSO-d_6) : δ = 26.4 (q, $C(\underline{C}H_3)_3$), 37.5 (s, $\underline{C}(CH_3)_3$), 117.8 (ds, $^2J_{CF}$ = 22 Hz, C-3a), 124.1 (dd, $^2J_{CF}$ = 28 Hz, C-5), 125.0 (d, $^3J_{CF}$ = 3 Hz, C-7a), 138.1 (dd, $^3J_{CF}$ = 10 Hz, C-6), 142.9 (ds, $^4J_{CF}$ = 2 Hz, C-7), 158.0 (ds, $^1J_{CF}$ = 267 Hz, C-4), 162.9 (s, CO), 176.1 (ds, $^3J_{CF}$ = 5

Hz, C-3). Anal. Calcd. for $C_{12}H_{12}FNO_4S$ (285.29) C 50.52; H 4.24; N 4.91; Calcd for $C_{12}H_{12}FNO_4S$*0.02 H_2O C 49.89; H 4.33; N 4.85. Found C 49.78; H 4.29; N 4.81.

4-Fluoro-3-(1,1-dimethylethyl)-benzo[d]-1,2-thiazole-1,1-dioxide-7-carboxylic acid methyl ester (5)

Two drops of conc. H_2SO_4 were added to a solution of **4g** (0.5 g, 1.75 mmol) in dry methanol (20 ml) and refluxed until TLC control showed complete esterification (approx.10 h). The solvent was then removed in vacuo, the residue dissolved in diethyl ether and washed with satd. $NaHCO_3$ and water. The organic phase was dried over Na_2SO_4, filtered, the solvent evaporated and the product recrystallized from diisopropyl ether. Yield: 0.45 g (86 %), colourless crystals, mp 213-215°C. ^{1}H NMR ($CDCl_3$): δ = 1.48 (s, 9H, $C(CH_3)_3$), 4.09 (s, 3H, OCH_3), 7.52 (dd, 1H, $^3J_{56}$ = 8 Hz, $^3J_{HF}$ = 10 Hz, H-5), 8.37 (dd, 1H, $^3J_{65}$ = 8 Hz, $^4J_{HF}$ = 4 Hz, H-6); ^{13}C NMR ($CDCl_3$): δ = 26.7 (q, $C(CH_3)_3$), 38.1 (s, $\underline{C}(CH_3)_3$), 53.3 (q, OCH_3), 118.9 (s, C-3a, $^2J_{CF}$ = 19 Hz), 123.0 (d, C-5, $^2J_{CF}$ = 28 Hz), 124.3 (s, $^3J_{CF}$ = 3 Hz, C-7a), 137.3 (d, $^3J_{CF}$ = 9 Hz, C-6), 144.7 (s, C-7), 159.0 (d, C-4, $^1J_{CF}$ = 268 Hz), 161.4 (s, CO), 176.4 (s, C-3).

3-Chloro-2-(2,2-dimethyl-1-oxopropyl)-benzenesulfonamide (6)

Yield: 72%, colourless crystals, mp 160-163°C. ^{1}H NMR ($CDCl_3$): δ = 1.30 (s, 9H, $C(CH_3)_3$), 7.38 (bs, 2H, NH_2), 7.52 (t, 1H, H-5, $J_{45,56}$ = 7.3 Hz), 7.63 (d, 1H, H-4, J_{45} = 7.3 Hz), 7.98 (d, 1H, H-6, J_{56} = 7.3 Hz); ^{13}C NMR ($CDCl_3$): δ = 28.3 (q, $C(\underline{C}H_3)_3$), 44.9 (s, $\underline{C}(CH_3)_3$), 126.2 (d, C-6), 129.3 (s, C-2), 129.4 (d, C-4*), 132.8 (d, C-5*), 137.4 (s, C-3), 142.1 (s, C-1), 210.9 (s, CO). Anal. Calcd. for $C_{11}H_{14}ClNO_3S$ (275.76) C 47.91; H 5.12; N 5.08. Found C 47.96; H 5.20; N 5.00.

4-Chloro-3-(1,1-dimethylethyl)-benzo[d]-1,2-thiazole-1,1-dioxide (4h)

Prepared by thermal dehydration of **6** at 170°C. Yield: 65%, colourless crystals, mp 134-136°C. ^{1}H NMR ($CDCl_3$): δ = 1.61 (s, 9H, $C(CH_3)_3$), 7.66 (t, 1H, H-6, $J_{56,67}$ = 7.3 Hz), 7.75 (d, 1H, H-5, J_{56} = 7.3 Hz), 7. (d, 1H, H-7, J_{67} = 7.3 Hz); ^{13}C NMR ($CDCl_3$): δ = 27.7 (q, $C(\underline{C}H_3)_3$), 38.3 (s, $\underline{C}(CH_3)_3$), 121.4 (d, C-7), 128.7 (s, C-3a), 131.2 (s, C-4), 133.9 (d, C-5*), 137.8 (d, C-6*), 143.7 (s, C-7a), 179.9 (s, C-3). Anal. Calcd. for $C_{11}H_{12}ClNO_2S$ (257.74) C 51.26; H 4.69; N 5.43. Found C 51.27; H 4.46; N 5.34.

4-Chloro-3-(1,1-dimethylethyl)-N-(1,1-dimethylethyl)-benzo[d]-1,2-thiazole-1,1-dioxide-7-carboxamide (4i)

Yield: 59%, colourless crystals, mp 118-122°C. ^{1}H NMR ($CDCl_3$): δ = 1.52 (s, 9H, $C(CH_3)_3$), 1.62 (s, 9H, $N(CH_3)_3$), 7.15 (bs, 1H, NH), 7.80 (d, 1H, H-5, J_{56} = 8.25 Hz), 8.07 (d, 1H, H-6, J_{65} = 8.25 Hz); ^{13}C NMR ($CDCl_3$): δ = 21.5 (q, $C(\underline{C}H_3)_3$*), 21.9 (q, $NHC(\underline{C}H_3)_3$*), 37.8 (s, $\underline{C}(CH_3)_3$), 52.1 (s, $NH\underline{C}(CH_3)_3$), 128.0 (s, C-3a), 132.1 (s, C-7*), 132.4 (s, C-4*), 133.9 (d, C-5), 137.6 (d, C-6), 140.0 (s, C-7a), 161.2 (s, CONH), 178.7 (s, C-3). Anal. Calcd. for $C_{16}H_{21}ClN_2O_3S$ (356.87) C 53.85; H 5.93; N 7.85. Found C 53.64; H 5.86; N 7.66.

4-Chloro-3-(1,1-dimethylethyl)-benzo[d]-1,2-thiazole-1,1-dioxide-7-phenylmethanol (4j)

Yield: 39%, colourless crystals, mp 132-136°C. ^{1}H NMR ($CDCl_3$): δ = 1.62 (s, 9H, $C(CH_3)_3$), 3.13 (bs, 1H, OH), 6.56 (s, 1H, CH), 7.28-7.41 (m, 3H, aromat. H), 7.49-7.58 (m, 2H, aromat. H), 7.6-7.7 (m, 2H, aromat. H); ^{13}C NMR ($CDCl_3$): δ = 27.8 (q, $C(\underline{C}H_3)_3$), 38.4 (s, $\underline{C}(CH_3)_3$), 70.0 (d, CHOH), 126.2 (d, C-2',6'), 128.1 (d, C-4'), 128.4 (s, C-3a), 128.6 (d, C-3',5'), 130.1 (s, C-7), 133.4 (d, C-5), 138.3

(d, C-6), 140.5 (s, C-4*), 140.7 (s, C-7a*), 180.1 (s, C-3). Anal. Calcd. for $C_{18}H_{18}ClNO_3S$ (363.86) C 59.42; H 4.99; N 3.85. Found C 59.18; H 4.87; N 3.75.

4-Chloro-3-(1,1-dimethylethyl)-7-methyl-benzo[d]-1,2-thiazole-1,1-dioxide (4k)

Yield: 60%, colourless crystals, mp 146-150°C. ^{1}H NMR ($CDCl_3$): δ = 1.60 (s, 9H, $C(CH_3)_3$), 2.70 (s, 3H, CH_3), 7.49 (d, 1H, H-5, J_{56} = 7.2 Hz), 7.69 (d, 1H, H-6, J_{65} = 7.2 Hz); ^{13}C NMR ($CDCl_3$): δ = 16.6 (q, CH_3), 27.7 (q, $C(\underline{C}H_3)_3$), 38.3 (s, $\underline{C}(CH_3)_3$), 128.2 (s, C-3a*), 128.6 (s, C-4*), 134.7 (s, C-7), 135.7 (d, C-5), 137.5 (d, C-6), 141.5 (s, C-7a), 179.9 (s, C-3). Anal. Calcd. for $C_{12}H_{14}ClNO_2S$ (271.77) C 53.04; H 5.19; N 5.15. Found C 52.99; H 5.15; N 5.09.

4-Chloro-3-(1,1-dimethylethyl)-benzo[d]-1,2-thiazole-1,1-dioxide-7-carboxylic acid (4l)

Yield: 49%, colourless crystals, mp 241-243°C. ^{1}H NMR (DMSO-d_6): δ = 1.55 (s, 9H, $C(CH_3)_3$), 8.10 (d, 1H, H-5, J_{56} = 8.7 Hz), 8.25 (d, 1H, H-6, J_{65} = 8.7 Hz), (bs, 1H, COOH); ^{13}C NMR (DMSO-d_6): δ = 27.7 (q, $C(\underline{C}H_3)_3$), 37.7 (s, $\underline{C}(CH_3)_3$), 127.3 (s, C-7a), 129.2 (s, C-3a), 134.2 (s, C-4), 135.3 (d, C-5*), 139.0 (d, C-6*), 143.0 (s, C-7), 163.1 (s, COOH), 176.5 (s, C-3). Anal. Calcd. for $C_{12}H_{12}ClNO_4S$ (301.75) C 47.77; H 4.01; N 4.64. Found C 47.78; H 3.94; N 4.55.

4-Chloro-3-(1,1-dimethylethyl)-benzo[d]-1,2-thiazole-1,1-dioxide-7-ol (4m)

Yield: 46%, colourless crystals, mp 256-259°C. ^{1}H NMR (DMSO-d_6): δ = 1.52 (s, 9H, $C(CH_3)_3$), 3.3 (bs, 1H, OH), 7.23 (d, 1H, H-5, J_{56} = 8.9 Hz), 7.68 (d, 1H, H-6, J_{56} = 8.9 Hz); ^{13}C NMR (DMSO-d_6): δ = 27.3 (q, $C(\underline{C}H_3)_3$), 37.7 (s, $\underline{C}(CH_3)_3$), 119.0 (s, C-4), 123.5 (d, C-6), 126.3 (s, C-3a), 129.0 (s, C-7a), 140.0 (d, C-5), 153.7 (s, C-7), 178.3 (s, C-3). Anal. Calcd. for $C_{11}H_{12}ClNO_3S$ (273.74) C 48.27; H 4.42; N 5.12; Calcd. for $C_{11}H_{12}ClNO_3S$*0.3 H_2O, C 47.33; H 4.55; N 5.02. Found C 47.38; H 4.26; N 4.96.

4-Chloro-3-(1,1-dimethylethyl)-benzo[d]-1,2-thiazole-1,1-dioxide-7-carbonitrile (4n)

Carboxamide **4i** (0.80 g, 2.24 mmol) was heated overnight with an excess of $POCl_3$ (10 ml). The reaction mixture was poured in ice-water, made alkaline with NaOH and extracted with ethyl acetate (200 ml). The combined organic layers were washed with saturated $NaHCO_3$ and water, dried over Na_2SO_4, the solvent evaporated and the residue recrystallized from diisopropyl ether. Yield: 0.34 g (54%) colourless crystals, mp 201-204°C. ^{1}H NMR ($CDCl_3$): δ = 1.61 (s, 9H, $C(CH_3)_3$), 7.87 (s, 2H, H-5,6); ^{13}C NMR ($CDCl_3$): δ = 27.7 (q, $C(\underline{C}H_3)_3$), 38.5 (s, $\underline{C}(CH_3)_3$), 106.8 (s, C-7), 112.2 (s, CN), 130.2 (s, C-3a), 135.8 (s, C-4), 136.1 (d, C-5), 138.4 (d, C-6), 146.3 (s, C-7a), 178.4 (s, C-3). Anal. Calcd. for $C_{12}H_{11}ClN_2O_2S$ (282.75) C 50.98; H 3.92; N 9.91. Found C 50.95; H 4.04; N 9.34.

6-Fluoro-7-(2,2-dimethyl-1-oxopropyl)-benzo[d]-1,2-thiazole-1,1-dioxide (7a)

Yield: 60%, colourless oil. ^{1}H NMR ($CDCl_3$) : δ = 1.31 (s, 9H, $C(CH_3)_3$), 7.47 (q, $^2J_{HF}$ = 8 Hz, J_{54} = 7 Hz, 1H, H-5), 7.71 (dd, $^3J_{HF}$ = 4 Hz, J_{45}= 7 Hz, 1H, H-4), 8.77 (s, 1H, H-3); ^{13}C NMR ($CDCl_3$) : δ = 26.7 (q, $C(\underline{C}H_3)_3$), 44.8 (s, $\underline{C}(CH_3)_3$), 121.7 (dd, $^2J_{CF}$ = 28 Hz, C-5), 126.9 (d, $^2J_{CF}$ = 25 Hz, C-7), 127.2 (s, C-3a), 128.2 (dd, $^3J_{CF}$ = 6 Hz, C-4), 138.3 (d, $^3J_{CF}$ = 3 Hz, C-7a), 161.1 (d, $^1J_{CF}$ = 265 Hz, C-6), 162.0 (d, C-3), 206.5 (s, CO).

6-Chloro-7-(2,2-dimethyl-1-oxopropyl)-benzo[d]-1,2-thiazole-1,1-dioxide (7b)

Yield: 65%, colourless crystals, mp 149-151°C. ^{1}H NMR ($CDCl_3$): δ = 1.4 (s, 9H, $C(CH_3)_3$), 7.61 (d, 1H, H-5, J_{54} = 8.25 Hz), 7.75 (d, 1H, H-4, J_{45} = 8.25 Hz), 8.78 (s, 1H, H-3). ^{13}C NMR ($CDCl_3$): δ = 27.4 (q, $C(\underline{C}H_3)_3$), 44.5 (s, $\underline{C}(CH_3)_3$), 126.7 (d, C-5), 129.0 (s, C-7), 135.5 (d, C-4), 136.0 (s, C-3a*),

136.3 (s, C-6*), 137.8 (s, C-7a*), 162.2 (d, C-3), 208.9 (s, CO). Anal. Calcd. for $C_{12}H_{12}ClNO_3S$ (285.75) C 50.44; H 4.23; N 4.90. Found C 50.23; H 4.25; N 4.79.

6-Chloro-7-(2,2-dimethyl-1-oxopropyl)-3-phenyl-benzo[d]-1,2-thiazole-1,1-dioxide (7c)

Yield: 63%, colourless crystals, mp 185-187°C. ^{1}H NMR ($CDCl_3$): δ = 1.44 (s, 9H, $C(CH_3)_3$), 7.58-7.84 (m, 5H, aromat. H), 7.89-7.96 (m, 2H, aromat. H); ^{13}C NMR ($CDCl_3$): δ = 27.4 (q, $C(\underline{C}H_3)_3$), 44.5 (s, $\underline{C}(CH_3)_3$), 126.8 (d, phenyl C-4*), 129.25 (d, phenyl C-2,6*), 129.3 (d, phenyl C-3,5*), 129.6 (s, C-7*), 133.6 (d, C-5), 134.6 (d, C-4), 135.6 (s, C-3a, phenyl C-1*), 138.1 (s, C-6), 138.4 (s, C-7a), 169.8 (d, C-3), 208.7 (s, CO). Anal. Calcd. for $C_{18}H_{16}ClNO_3S$ (361.85) C 59.75; H 4.46; N 3.87. Found C 59.49; H 4.35; N 3.84.

6-Chloro-7-(2,2-dimethyl-1-oxopropyl)-2,3-dihydro-benzo[d]-1,2-thiazole-1,1-dioxide (8)

A solution of **7b** (0.57 g, 1.99 mmol) in ethanol (10 ml) was treated with $NaBH_4$ (0.038 g, 1.00 mmol, 0.5 equiv) and stirred for 5 h at room temperature. The reaction mixture was poured in 2n HCl and extracted with ethyl acetate. The combined extracts were dried over Na_2SO_4, the solvent evaporated and the residue washed with diisopropyl ether. Yield: 0.51 g (89%), colourless crystals, mp 179-182°C. ^{1}H-NMR (DMSO-d6): δ = 1.29 (s, 9H, $C(CH_3)_3$), 4.40 (d, 2H, H-3, $^3J_{HH}$ = 6.0 Hz), 7.64 (d, 1H, H-5, J_{54} = 9.5 Hz), 7.86 (d, 1H, H-4, J_{45} = 9.5 Hz), 8.12 (t, 1H, NH, $^3J_{HH}$ = 6.0 Hz); ^{13}C-NMR (DMSO-d6): δ = 27.1 (q, $C(\underline{C}H_3)_3$), 43.9 (s, $\underline{C}(CH_3)_3$), 44.2 (t, C-3), 127.3 (d, C-4), 127.8 (s, C-6), 133.6 (d, C-5), 133.9 (s, C-7*), 134.3 (s, C-3a*), 138.6 (s, C-7a*), 209.4 (s, CO). Anal. Calcd. for $C_{12}H_{14}ClNO_3S$ (287.77) C 50.08; H 4.90; N 4.87. Found C 50.05; H 4.99; N 4.66.

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