Regiospecific Synthesis of 2-Methyl-4-arylcarbonyl-2*H*-1,2-benzothiazin-3(4*H*)-one 1,1-Dioxides

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Acylation of 2-methyl-2*H*-1,2-benzothiazin-3(4*H*)-one 1,1-dioxide **3** with aryl anhydrides in the presence of dimethylaminopyridine occurs regiospecifically to afford 2-methyl-4-arylcarbonyl-2*H*-1,2-benzothiazin-3(4*H*)-one 1,1-dioxides **2a-f**.

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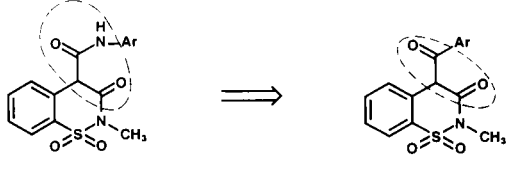
The three key parameters associated with the design of a nonsteroidal antiinflammatory drug (NSAID) are recognized to be a planar structure, moderate lipophilicity and acidity. The acidic functional group (p*K*a 3-6) of a NSAID is largely ionized in the plasma (*p*H 7.4) where it becomes protein bound. However, at the site of inflammation, a metabolic drop in *p*H causes an equilibrium shift to the unionized drug which penetrates into the site of inflammation [1]. Acidic NSAID's form three chemical structural classes; carboxylic acids, pyrazoles and oxicams (2-methyl-1,2-benzothiazine 1,1-dioxides) [2]. The acidic functional group present in the oxicam class is a β-ketoamide, as in 2-methyl-*N*-aryl-2*H*-1,2-benzothiazin-3(4*H*)-one-4-carboxamide 1,1-dioxide **1** (Figure 1) [3]. This family of oxicam β-ketoamides is acidic (p*K*a 5-6) and has antiinflammatory activity up to 1.5 times that of the classical nonsteroidal antiinflammatory drug, indomethacin [3].

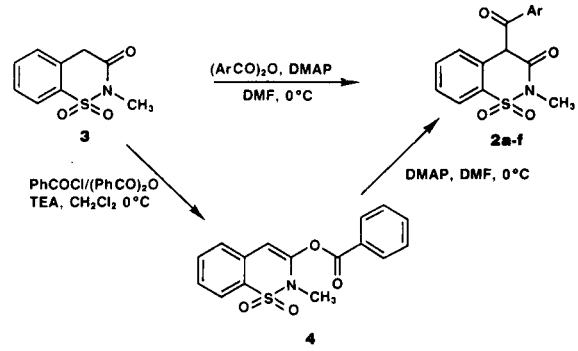
FIGURE 1



1 **2a-f**

Since **1** is potent NSAID [3], we wished to prepare analogs of **1** by replacing the carboxamide functionality with a ketone group to give 2-methyl-4-arylcarbonyl-2*H*-1,2-benzothiazin-3(4*H*)-one 1,1-dioxides **2a-f** (Figure 1). This substitution would retain the acidic β-diketo moiety necessary for the antiinflammatory activity found in **1**, while broadening the structure-activity relationships (SAR). Our synthetic route to **2a-f** was to acylate regiospecifically the readily available 2-methyl-2*H*-1,2-benzothiazin-3(4*H*)-one 1,1-dioxide **3** (Scheme 1) [3,4]. Unfortunately acylation of **3** with benzoic anhydride or benzoyl chloride in the presence of triethylamine gave the *O*-acylated regioisomer, 2-methyl-3-benzoyloxy-2*H*-1,2-benzothiazine 1,1-dioxide **4**. The use of sodium hydride or pyridine as bases in solvents such as dimethylformamide, tetrahydrofuran or pyridine similarly afforded **4**.

Scheme 1

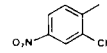


Since we were unable to obtain **2a** directly from **3** *via* regiospecific acylation, we then focused our efforts at transforming **4** into **2a**. An analogous transformation had been previously achieved in the rearrangement of 5-acyloxyoxazoles to 4-acyl-2-oxazolin-5-ones, catalyzed by dimethylaminopyridine [5]. We reasoned that the benzoyl group in **4** might similarly be transferred by dimethylaminopyridine to give **2a**. Thus, reaction of **4** with dimethylaminopyridine gave the *C*-acylated regioisomer, **2a** (Scheme 1).

In order to prepare analogs of **2a** directly from **3**, we desired an *in situ* two step reaction sequence in which **4** would be initially formed followed by rearrangement *via* acyl transfer to **2a**. Thus, reaction of **3** with benzoic anhydride in the presence of dimethylaminopyridine gave **2a**. Similarly **2b-f** were prepared by reaction of **3** with aryl anhydrides [6] in the presence of dimethylaminopyridine in yields ranging from 40-56% (Table 1).

Having secured an efficient and regiospecific route to **2a-f**, we next turned our attention towards elucidating the tautomeric structure of **2a-f**. A single crystal X-ray crystallographic analysis of **2d** reveals an enol tautomeric structure (Figure 2). Since acidity is an important physicochemical property associated with antiinflammatory activity, we carried out p*K*a determinations of **2a-f**. Analogs **2a-f** possess a p*K*a 5-8 [7] which is similar to the p*K*a of **1** (p*K*a 5-6).

Table 1
4-ARYLCARBONYLBENZOTHIAZINES **2a-f**

No.	Ar	Yield (%)	pKa
2a		46	8.0
2b		49	6.7
2c		53	5.4
2d		56	5.4
2e		43	6.1
2f		40	7.1

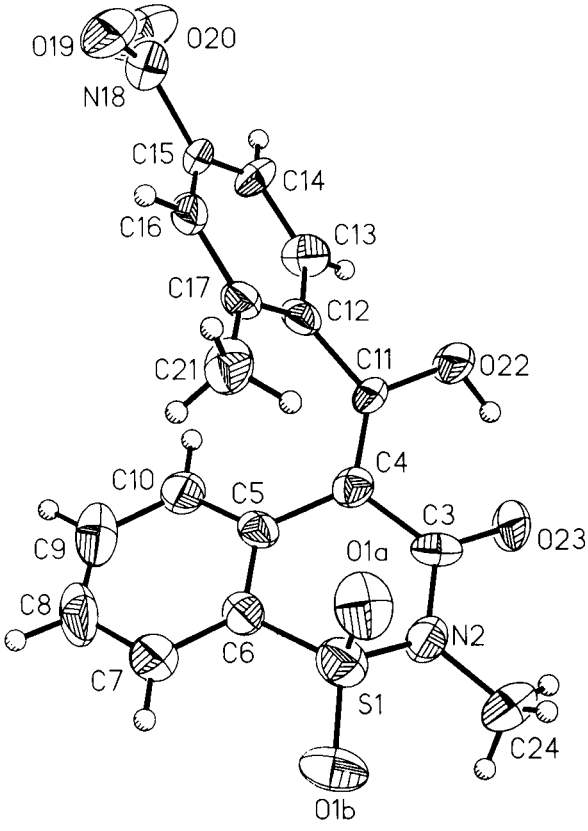


Figure 2
X-RAY STRUCTURE OF **2d**

In conclusion, two regiospecific acylations of **3** have been developed. Acylation of **3** with benzoic anhydride or benzoyl chloride in the presence of triethylamine yields **4**. Acyl transfer of the 3-benzoyl group in **4** with dimethylaminopyridine gives **2a**. Thus, acylation of **3** with aryl anhydrides in the presence of dimethylaminopyridine and concomitant acyl transfer affords **2a-f**. Compounds **2a-f** are weakly acidic (p*k*a 5-8) and exist as an enol tautomer. In contrast to **1**, **2a-f** are devoid of antiinflammatory activity.

EXPERIMENTAL

Melting points were determined on a Thomas Hoover Melting Point Apparatus and are uncorrected. Proton nmr spectra were recorded on a Bruker-WM250 or Varian EM-390 spectrometer. Mass spectra were recorded on a Finnigan 4510 spectrometer at 70eV. Infrared spectra were recorded on a Perkin Elmer 383B spectrophotometer. Elemental analysis was recorded on a Control Equipment Corp. 240XA CHN analyzer.

2-Methyl-3-benzoyloxy-2*H*-1,2-benzothiazine 1,1-Dioxide (**4**).

To a stirred solution of **3** (1.00 g, 4.73 mmoles) in 40 ml of dry methylene chloride at 0° was added triethylamine (1.39 ml, 9.93 mmoles). The mixture was stirred at 0° for 15 minutes, then a solution of benzoyl chloride (0.60 ml, 5.20 mmoles) in 10 ml of dry methylene chloride was added dropwise. The reaction mixture was allowed to slowly warm to room temperature over 4 hours, washed with water, brine, dried (magnesium sulfate) and concentrated *in vacuo* to afford the crude product. Chromatography on silica gel using methylene chloride as eluant gave 1.40 g of white solid. Recrystallization from toluene:hexane gave **4** (1.28 g) in a yield of 86% mp 123-125°; ms: m/e 315 (M^+, 13), 105 (100); ^{1}H-nmr (deuteriochloroform): δ 8.16 (d, 2H), 7.88 (d, 1H), 7.66 (t, 1H), 7.58-7.40 (m, 5H), 6.38 (s, 1H), 3.27 (s, 3H); ir (potassium bromide): ν CO 1754 cm^{-1}.

Anal. Calcd. for $C_{16}H_{13}NO_4S$: C, 60.94; H, 4.16; N, 4.44. Found: C, 60.57; H, 4.16; N, 4.44. Mass Spectrum Calcd. for $C_{16}H_{13}NO_4S$ m/e 315.0565. Found: 315.0558.

2-Methyl-4-benzoyl-2*H*-1,2-benzothiazin-3(4*H*)-one 1,1-Dioxide (**2a**).

To a stirred solution of **4** (500 mg, 1.59 mmoles) in 10 ml of dry dimethylformamide at 0° was added dimethylaminopyridine (203 mg, 1.66 mmoles). The reaction mixture was allowed to slowly warm to room temperature, then stirred for 48 hours. The reaction mixture was poured into an aqueous acid:ice mixture and stirred for 1 hour. The precipitate was filtered, washed with water (40 ml), and dried to give 0.47 g of crude product. Chromatography on silica gel using ethyl acetate:methylene chloride (1:19) as eluant afforded **2a** (243 mg) in a yield of 49% as an amber oil which crystallized upon standing mp 91-93°; ms: m/e 315 (M^+, 74), 237 (38), 105 (100); ^{1}H-nmr (deuteriochloroform): δ 7.88 (dd, 1H), 7.61-7.14 (m, 7H), 6.83 (d, 1H), 3.39 (s, 3H); ir (potassium bromide): ν OH 3432, ν CO 1605, 1570 cm^{-1}.

Anal. Calcd. for $C_{16}H_{13}NO_4S$: C, 60.94; H, 4.16; N, 4.44. Found: C, 60.92; H, 4.06; N, 4.47: Mass Spectrum Calcd. for $C_{16}H_{13}NO_4S$ m/e 315.0565. Found: 315.0560.

Preparation of 4-Arylcarbonylbenzothiazines **2a-f** *via* Regiospecific Acylation of Benzothiazine **3**.

General Procedure.

To a stirred solution of **3** (500 mg, 2.37 mmoles) and dimethylaminopyridine (636 mg, 5.21 mmoles) in 10 ml of dry dimethyl-

formamide at 0° was added dropwise a solution of anhydride (2.84 mmole) in 5 ml of dry dimethylformamide. The reaction mixture was stirred at 0° for 30 minutes, warmed to room temperature, then stirred overnight. The reaction mixture was poured into an aqueous acid:ice mixture and stirred for 1 hour. The resulting suspension was filtered and the filtrant washed with water and dried to give crude product. Chromatography on silica gel using ethyl acetate:methylene chloride (1:19) as eluant gave pure 4-arylcarbonylbenzothiazines **2a-f**. Recrystallization from an appropriate solvent gave an analytically pure compound.

2-Methyl-4-benzoyl-2*H*-1,2-benzothiazin-3(4*H*)-one 1,1-Dioxide (**2a**).

This compound was obtained in 46% yield as white crystals (toluene:hexane) mp 95-98°; ms: m/e 315 (M^+, 35), 237 (19), 105 (100); ^{1}H-nmr (deuteriochloroform): δ 7.90 (d, 1H), 7.60-7.16 (m, 7H), 6.84 (d, 1H), 3.38 (s, 3H); ir (potassium bromide): ν OH 3426, ν CO 1609, 1591 cm^{-1}.

Anal. Calcd. for $C_{16}H_{13}NO_4S$: C, 60.94; H, 4.16; N, 4.44. Found: C, 61.25; H, 4.10; N, 4.41.

2-Methyl-4-(4-chlorobenzoyl)-2*H*-1,2-benzothiazin-3(4*H*)-one 1,1-Dioxide (**2b**).

This compound was obtained in a 49% yield as white crystals (toluene:hexane) mp 130-133°; ms: m/e 349 (M^+, 100), 237 (65), 141 (29), 139 (88), 111 (40); ^{1}H-nmr (deuteriochloroform): δ 7.92 (d, 1H), 7.54 (d, 2H), 7.38-7.20 (m, 5H), 6.86 (d, 1H), 3.38 (s, 3H); ir (potassium bromide): ν OH 3428, ν CO 1635, 1599 cm^{-1}.

Anal. Calcd. for $C_{16}H_{12}ClNO_4S$: C, 60.94; H, 4.16; N, 4.44. Found: C, 61.25; H, 4.10; N, 4.41.

2-Methyl-4-(4-nitrobenzoyl)-2*H*-1,2-benzothiazin-3(4*H*)-one 1,1-Dioxide (**2c**).

This compound was obtained in a 53% yield as white crystals (toluene) mp 205-207°; ms: m/e 360 (M^+, 100), 343 (46), 150 (32); ^{1}H-nmr (deuteriochloroform): δ 8.22 (d, 2H), 7.94 (d, 1H), 7.78 (d, 2H), 7.34 (t, 1H), 7.24 (t, 2H), 6.78 (d, 1H), 3.40 (s, 3H); ir (potassium bromide): ν OH 3438, ν CO 1626, 1579 cm^{-1}.

Anal. Calcd. for $C_{16}H_{12}N_2O_6S$: C, 53.33; H, 3.36; N, 7.77. Found: C, 53.58; H, 3.37; N, 8.02.

2-Methyl-4-(2-methyl-4-nitrobenzoyl)-2*H*-1,2-benzothiazin-3(4*H*)-one 1,1-Dioxide (**2d**).

This compound was obtained in a 56% yield as white crystals (toluene:hexane) mp 167-170°; ms: m/e 374 (M^+, 84), 211 (53), 164 (22); ^{1}H-nmr (deuteriochloroform): δ 8.08 (m, 2H), 7.92 (d, 1H), 7.62 (d, 1H), 7.38-7.24 (m, 3H), 6.56 (d, 1H), 3.42 (s, 3H), 2.34 (s, 3H); ir (potassium bromide): ν OH 3426, ν CO 1621, 1580 cm^{-1}.

Anal. Calcd. for $C_{17}H_{14}N_2SO_6$: C, 54.54; H, 3.77; N, 7.48. Found: C, 54.66; H, 3.72; N, 7.34.

2-Methyl-4-(3-trifluoromethylbenzoyl)-2*H*-1,2-benzothiazin-3(4*H*)-one (**2e**).

This compound was obtained in a 43% yield as white crystals (toluene:hexane) mp 133-135°; ms: m/e 383 (M^+, 100), 289 (32), 173 (83), 145 (44); ^{1}H-nmr (deuteriochloroform): δ 7.94 (d, 2H), 7.72 (m, 2H), 7.44 (t, 1H), 7.28 (m, 3H), 6.80 (d, 1H), 3.40 (s, 3H); ir (potassium bromide): ν OH 3446, ν CO 1621, 1577 cm^{-1}.

Anal. Calcd. for $C_{17}H_{12}NO_4SR_3$: C, 53.27; H, 3.16; N, 3.65. Found: C, 53.26; H, 3.16; N, 3.46.

2-Methyl-4-(2-Furoyl)-2*H*-1,2-benzothiazin-3(4*H*)-one 1,1-Dioxide (**2f**).

This compound was obtained in a 40% yield as white crystals (toluene:hexane) mp 113-115°; ms: m/e 305 (M^+, 53), 237 (85), 95 (100); ^{1}H nmr (deuteriochloroform): δ 7.92 (d, 1H), 7.40 (m, 3H), 7.22 (d, 1H), 7.06 (d, 1H), 6.58 (m, 1H), 3.36 (s, 3H); ir (potassium bromide): ν OH 3414, ν CO 1615, 1598 cm^{-1}.

Anal. Calcd. for $C_{14}H_{11}NO_5S$: C, 55.08; H, 3.63; N, 4.59. Found: C, 55.01; H, 3.65; N, 4.57.

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[7] p*ka* determinations were performed in dioxane:water (2:1).