A Microwave Induced Cyclisation of α-Phenylsulfonyl-Enaminoacrylates for the Preparation of 4-Aryl-4*H*-1,4-Benzothiazine 1,1-Dioxide Derivatives

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Several 4-aryl-4H-1,4-benzothiazine 1,1-dioxide derivatives have been prepared in good yields by microwave promoted cyclisation of α-phenylsulfonyl-enaminoacrylate intermediates in basic media. Benzothiazines were obtained without the use of a catalyst in short reaction times.

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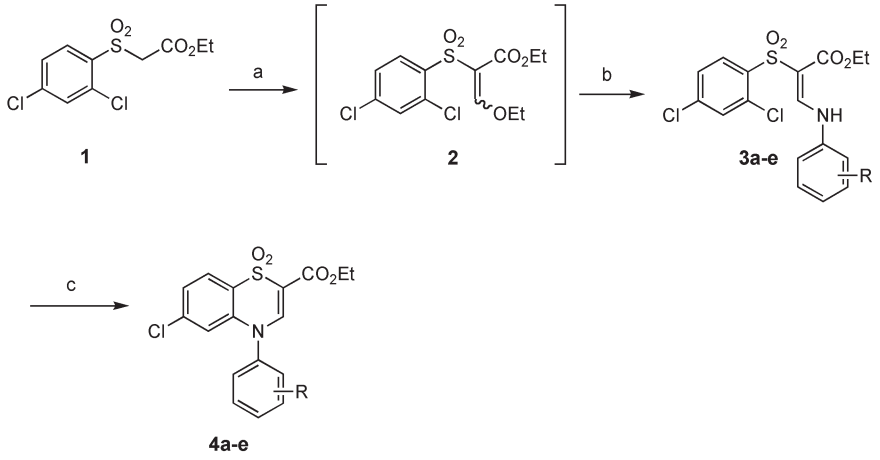
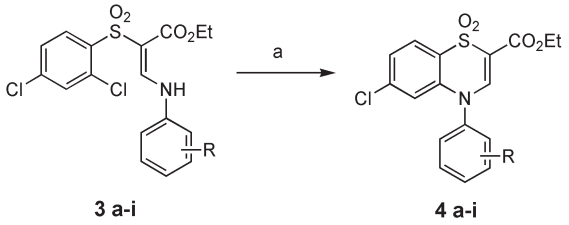
During the course of our research toward the synthesis of novel 4-aryl-4*H*-1,4-benzothiazine 1,1-dioxide derivatives [1-3], we decided to explore some new alternatives for the crucial cyclisation step of the α-phenylsulfonyl enaminoacrylate intermediates to the corresponding benzothiazines. Despite this kind of cyclisation is relatively easy for their isostere counterpart α-phenylcarbonyl enaminoacrylates for the synthesis of 1-arylquinolones by the widely employed Groche's methodology [4], it was not achieved in high yields for the preparation of 4-aryl substituted 1,4-benzothiazines unless a 5% silver nitrate was used as a catalyst (Scheme 1) [2]. The silver nitrate, may complex the chlorine atom of the aromatic ring lowering the energy of the transition state of the aromatic substitution bringing the reaction to completion in high yields. Recently, a great interest in microwave promoted reactions has emerged in organic synthesis [5], it has been used for the preparation of heterocycles [5-10] and valuable organic intermediates in short reaction times without the use of costly reagents and catalysts. This available technology has led us to test microwave irradiation for the synthesis of organofluorine aromatic amides [11] and the cyclisation of enaminoacrylates to 4-aryl-4*H*-1,4-benzothiazines (**4 a-i**) without the aid of catalyst (Scheme 2), standard conditions were established varying the microwave power source and the reaction time (Table 1). Our results show that microwave irradiation is a good alternative for the cyclisation step instead of use of a catalyst. Although a slightly lower, comparable yields of the benzothiazines were obtained and the methodology is also affordable even for the cyclisation of hindered *ortho*-substituted acrylates (**3f**, **3i**). In view that nucleophilic aromatic substitution (S_NAr) reactions have not been explored much under microwave irradiation conditions [12], this work represents a new contribution to the knowledge of the application of microwave synthesis to achieve this goal efficiently in short reaction times.

Scheme 1



Conditions: a. $HC(OEt)_3$, acetic anhydride, reflux, 3h ; b. substituted anilines, ethanol, H_2SO_4 cat., reflux, 2h; c. potassium carbonate (1.2 equiv.), silver nitrate (5% mole)/dimethylformamide, reflux, 2h.

Scheme 2



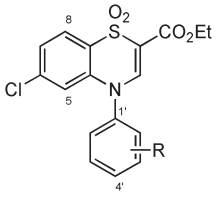
Conditions: a. potassium carbonate (1.2 equiv.), dimethyl-formamide, mw irradiation.

fonylacetate (**1**) and enaminoacrylates (**3 a-e**) were prepared according to the literature procedure [2].

General Procedure for the Preparation of Ethyl 2-(2,4-Dichlorophenylsulfonyl)-3-(substituted-anilino)-acrylates (**3 f-i**).

A mixture of **1** (2.0 g, 6.73 mmol), acetic anhydride (1.5 g, 10.10 mmol) and triethylorthoformate (1.65 g, 16.15 mmol) was stirred under reflux using a *Dean–Stark* trap for 3 h. The solvent was removed *in vacuo* and the remaining oil was directly used for the next step. Thus, it was dissolved in ethanol (50 mL), treated first with the substituted aniline (6.73 mmol) and subsequently with one drop of concentrated sulfuric acid. The reaction mixture was then stirred under reflux for 2 h and allowed to cool at room temperature. The formed solid was filtered, washed with ethanol, and dried *in vacuo* to give (**3 f-i**).

Table 1



4 a-i

Compound	R	Melting point (°C)	Yield (%)	Yield (%) [b] using catalyst	MW power (watts)	Irradiation time (s)
4a	4'-Br	[a]	76	85	600	240
4b	4'-Cl	[a]	78	82	600	300
4c	3'-Cl	[a]	74	80	600	200
4d	4'-OMe	[a]	82	90	600	240
4e	4'-F	[a]	69	71	600	300
4f	2'-OMe	164-166	74	[c]	600	240
4g	4'-Me	201-203	78	[c]	600	200
4h	3',5'-Cl_2	220-222	71	[c]	600	160
4i	2'-Cl	213-214	70	[c]	600	160

[a] Similar to that found in our reported procedure [2]; [b] Potassium carbonate (1.2 equiv), silver nitrate (5% mole)/dimethylformamide, 100 °C, 2 h; [c] New compounds, not previously synthesized using silver nitrate as catalyst.

EXPERIMENTAL

Melting points were determined in a Fischer-Johns micro hot-stage apparatus and are uncorrected. MW irradiation was made with a GoldStar microwave conventional oven, model MA-690M (600 W, 2450 MHz). NMR spectra were obtained on a JEOL Eclipse Plus spectrometer in deuterated chloroform, operating at 400 MHz (^{1}H, internal standard TMS) and 100 MHz (^{13}C, internal standard TMS); δ values in ppm relative to the internal standard are given. The IR spectra were recorded as potassium bromide discs using a Shimadzu CW/IR 470 spectrometer. Elemental analyses were performed by Atlantic Microlab Inc. (Norcross, GA, USA); results fell in the range of ± 0.4% of the required theoretical values. Silica gel plates ALUGRAM® SIL G/UV254 (Macherey-Nagel GmbH & Co., Germany) were used for TLC testing. Reagents were obtained from Aldrich (Milwaukee, MI, USA) or Merck (Darmstadt, Germany) and used without further purification. Ethyl 2,4-dichlorophenyl-sul-

Ethyl 2-(2,4-Dichlorophenylsulfonyl)-3-(2-methoxyanilino)-acrylate (**3f**).

This compound was obtained as a yellow solid, 1.79 g (62%), mp 190-192 °C; ^{1}H nmr (deuteriochloroform): δ 1.11 (t, 3H, CH_3), 3.93 (s, 3H, OCH_3), 4.12 (c, 2H, CH_2), 6.96 (d, 1H, ar-H, *J*=8.4 Hz), 7.02 (t, 1H, ar-H, *J*=8.1 Hz), 7.16 (ddd, 1H, ar-H, *J*=1.5 Hz, *J*=7.9 Hz), 7.31 (d, 1H, ar-H, *J*=7.4 Hz), 7.40 (dd, 1H, 5'-H, *J*=2.2 Hz, *J*=8.6 Hz), 7.44 (d, 1H, 3'-H, *J*=2.2 Hz), 8.22 (d, 1H, 6'-H, *J*=8.6 Hz), 8.67 (d, 1H, vinyl-H, *J*=14.3 Hz), 10.92 (d, 1H, NH, *J*=14.3 Hz); ^{13}C nmr (deuteriochloroform): δ 13.98, 56.07, 60.91, 100.46, 111.50, 115.05, 121.45, 126.05, 126.91, 127.93, 131.27, 132.89, 133.69, 137.58, 139.38, 149.15, 151.32, 164.80; ir (potassium bromide): 3340 (NH), 1696 (CO), 1622 (C=C), 1337, 1302, 1155 and 1142 (SO_2) cm^{-1}.

Anal. Calcd. for $C_{18}H_{17}Cl_2NO_5S$: C, 50.24; H, 3.98; N, 3.26. Found: C, 50.18; H, 4.02; N, 3.20.

Ethyl 2-(2,4-Dichlorophenylsulfonyl)-3-(4-methylanilino)-acrylate (**3g**).

This compound was obtained as a creamy solid, 1.18 g (65%) mp 178-180 °C; ^{1}H nmr (deuteriochloroform): δ 1.08 (t, 3H, CH_3), 2.35 (s, 3H, CH_3), 4.10 (c, 2H, CH_2), 7.07 (d, 2H, ar-H, *J*=8.4 Hz), 7.20 (d, 2H, ar-H, *J*=8.4 Hz), 7.40 (dd, 1H, 5'-H, *J*=2.2 Hz, *J*=8.4 Hz), 7.45 (d, 1H, 3'-H, *J*=2.2 Hz), 8.21 (d, 1H, 6'-H, *J*=8.4 Hz), 8.62 (d, 1H, vinyl-H, *J*=13.9 Hz), 10.70 (d, 1H, NH, *J*=13.9 Hz); 3345 (NH), 1691 (CO), 1630 (C=C), 1325, 1248, 1150 and 1136 (SO_2) cm^{-1}.

Anal. Calcd. for $C_{18}H_{17}Cl_2NO_4S$: C, 52.18; H, 4.14; N, 3.38. Found: C, 52.24; H, 4.11; N, 3.42.

Ethyl 2-(2,4-Dichlorophenylsulfonyl)-3-(3,5-dichloroyanilino)-acrylate (**3h**).

This compound was obtained as a yellow solid, 1.89 g (60%), mp 215-216 °C; ^{1}H nmr (deuteriochloroform): δ 1.10 (t, 3H, CH_3), 4.10 (c, 2H, CH_2), 7.08 (m, 2H, ar-H), 7.19 (t, 1H, ar-H, *J*=1.44 Hz), 7.42 (dd, 1H, 5'-H, *J*=1.8 Hz, *J*=8.8 Hz), 8.54 (d, 1H, vinyl-H, *J*=13.5 Hz), 10.71 (d, 1H, NH, *J*=13.5 Hz); ^{13}C nmr (deuteriochloroform): δ 13.87, 56.07, 61.44, 116.13, 125.77, 127.08, 131.44, 133.71, 136.67, 136.82, 139.90, 140.42, 152.03, 164.94; ir (potassium bromide): 3350 (NH), 1664 (CO), 1632 (C=C), 1315, 1240, 1155 and 1145 (SO_2) cm^{-1}.

Anal. Calcd. for $C_{17}H_{13}Cl_4NO_4S$: C, 43.52; H, 2.79; N, 2.99. Found: C, 43.49; H, 2.75; N, 3.04.

Ethyl 2-(2,4-Dichlorophenylsulfonyl)-3-(2-chloroanilino)-acrylate (**3i**).

This compound was obtained as a yellow solid, 1.96 g (67%), mp 164-166 °C; ^{1}H nmr (deuteriochloroform): δ 1.12 (t, 3H, CH_3), 4.14 (c, 2H, CH_2), 7.15 (m, 1H, ar-H), 7.40 (m, 5H, ar-H), 8.22 (d, 1H, 6'-H, *J*=8.4 Hz), 8.67 (d, 1H, vinyl-H, *J*=13.6 Hz), 11.10 (d, 1H, NH, *J*=13.6 Hz); ^{13}C nmr (deuteriochloroform): δ 13.97, 61.30, 102.37, 116.26, 124.13, 126.21, 127.04, 128.46, 130.47, 131.37, 132.91, 133.74, 135.69, 137.18, 139.70, 151.54, 164.75; ir (potassium bromide): 3264 (NH), 1676 (CO), 1615 (C=C), 1337, 1302, 1155 and 1142 (SO_2) cm^{-1}.

Anal. Calcd. for $C_{17}H_{14}Cl_3NO_4S$: C, 46.97; H, 3.25; N, 3.22. Found: C, 47.01; H, 3.22; N, 3.27.

General Procedure for the Preparation of Ethyl 4-(Substituted-phenyl)-6-chloro-4*H*-1,4-benzothiazine-2-carboxylate-1,1-dioxides (**4 a-i**).

A mixture of the corresponding acrylate **3 a–i** (1.0 mmol), powdered potassium carbonate (1.2 mmol) and dimethylformamide (5 mL) in a 25 mL capped conical flask was put into a teflon cylinder container (5 cm diameter x 15 cm height) and microwave irradiated at several stages (30–40 seg each) to complete the indicated time. After being cooled to room temperature, to the resulting mixture was added an amount of ice-water to precipitate the products which were then collected by filration and washed with cool water. All products were obtained in high purity as indicated by TLC and ^{1}H NMR analysis.

Ethyl 4-(2-Methoxy-phenyl)-6-chloro-4*H*-1,4-benzothiazine-2-carboxylate-1,1-dioxide (**4 f**).

This compound was obtained as a creamy solid, 0.29 g (74%), mp 164-166 °C; ^{1}H nmr (deuteriochloroform): δ 1.39 (t, 3H, CH_3), 3.79 (s, 3H, OCH_3), 4.41 (c, 2H, CH_2), 6.53 (s, 1H, 5-H), 7.14 (m, 2H, ar-H), 7.30 (m, 2H, ar-H), 7.57 (t, 1H, ar-H, *J*=8.1 Hz), 7.82 (s, 1H, 3-H), 8.09 (d, 1H, 8-H, *J*=8.4 Hz); ^{13}C nmr (deuteriochloroform): δ 14.34, 55.99, 62.11, 106.88, 112.94, 117.11, 121.88, 121.95, 126.84, 126.02, 127.45, 128.37, 129.05, 132.25, 138.27, 154.88, 161.12.; ir (potassium bromide): 1702 (CO), 1350, 1292, 1142 and 1104 (SO_2) cm^{-1}.

Anal. Calcd. for $C_{18}H_{16}ClNO_5S$: C, 54.89; H, 4.09; N, 3.56. Found: C, 54.82; H, 4.11; N, 3.50.

Ethyl 4-(4-Methyl--phenyl)-6-chloro-4*H*-1,4-benzothiazine-2-carboxylate-1,1-dioxide (**4g**).

This compound was obtained as a creamy solid, 0.29 g (78%), mp 201-203 °C; ^{1}H nmr (deuteriochloroform): δ 1.39 (t, 3H, CH_3), 2.48 (s, 3H, CH_3), 4.39 (c, 2H, CH_2), 6.65 (d, 1H, 5-H, *J*=8.4 Hz), 7.22 (d, 2H, ar-H, *J*=8.1 Hz), 7.33 (dd, 1H, 7-H, *J*=1.5 Hz, *J*=8.4 Hz), 7.42 (d, 2H, ar-H, *J*=8.1 Hz), 7.92 (s, 1H, 3-H), 8.10 (d, 1H, 8-H, *J*=8.4 Hz). ir (potassium bromide): 1705 (CO), 1335, 1267, 1144 and 1126 (SO_2) cm^{-1}.

Anal. Calcd. for $C_{18}H_{16}ClNO_4S$: C, 57.22; H, 4.27; N, 3.71. Found: C, 57.29; H, 4.22; N, 3.67.

Ethyl 4-(3,5-Dichloro-phenyl)-6-chloro-4*H*-1,4-benzothiazine-2-carboxylate-1,1-dioxide (**4 h**).

This compound was obtained in 71% yield (0.31g), mp 220-222 °C; ^{1}H nmr (deuteriochloroform): δ 1.39 (t, 3H, CH_3), 3.79 (s, 3H, OCH_3), 4.41 (c, 2H, CH_2), 6.53 (s, 1H, 5-H), 7.14 (m, 2H, ar-H), 7.30 (m, 2H, ar-H), 7.57 (t, 1H, ar-H, *J*=8.1 Hz), 7.82 (s, 1H, 3-H), 8.09 (d, 1H, 8-H, *J*=8.4 Hz); ^{13}C nmr (deuteriochloroform): δ 14.34, 55.99, 62.11, 106.88, 112.94, 117.11, 121.88, 121.95, 126.84, 126.02, 127.45, 128.37, 129.05, 132.25, 138.27, 154.88, 161.12. ir (potassium bromide): 1703 (CO), 1350, 1296, 1152, and 1107 (SO_2) cm^{-1}.

Anal. Calcd. for $C_{17}H_{12}Cl_3NO_4S$: C, 47.19; H, 2.80; N, 3.24. Found: C, 47.23; H, 2.83; N, 3.26.

Ethyl 4-(2-Chloro-phenyl)-6-chloro-4*H*-1,4-benzothiazine-2-carboxylate-1,1-dioxide (**4i**).

This compound was obtained as a creamy solid, 0.28 g (70%), mp 213-214 °C; ^{1}H nmr (deuteriochloroform): δ 1.39 (t, 3H, CH_3), 3.79 (s, 3H, OCH_3), 4.41 (c, 2H, CH_2), 6.53 (s, 1H, 5-H), 7.14 (m, 2H, ar-H), 7.30 (m, 2H, ar-H), 7.57 (t, 1H, ar-H, *J*=8.1 Hz), 7.82 (s, 1H, 3-H), 8.09 (d, 1H, 8-H, *J*=8.4 Hz); ^{13}C nmr (deuteriochloroform): δ 14.34, 55.99, 62.11, 106.88, 112.94, 117.11, 121.88, 121.95, 126.84, 126.02, 127.45, 128.37, 129.05, 132.25, 138.27, 154.88, 161.12. ir (potassium bromide): 1705 (CO), 1350, 1299, 1142 and 1107 (SO_2) cm^{-1}.

Anal. Calcd. for $C_{17}H_{13}Cl_2NO_4S$: C, 51.27; H, 3.29; N, 3.52. Found: C, 51.20; H, 3.23; N, 3.58.

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