N-Benzoyl-*N*-methylsulfonylanthranilates: unexpected cyclization reaction to 4-alkoxy-2,1-benzothiazines

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DOI: http://dx.doi.org/10.3998/ark.5550190.0012.912

Abstract

The synthesis of 4-alkoxy-1*H*-2,1-benzothiazine 2,2-dioxide derivatives was achieved through an unexpected base-mediated cyclization of *N*-benzoyl-*N*-methylsulfonylanthranilates. A reaction mechanism involving the sulfene species has been postulated. The obtained 4-alkoxy derivatives can be further functionalized at the N-1 position allowing unsymmetrically *N*,*O*-disubstituted 1*H*-2,1-benzothiazines 2,2-dioxide to be prepared.

Keywords: 4-Alkoxy-1*H*-2,1-benzothiazine 2,2-dioxide, *N*-benzoyl-*N*-methylsulfonyl-anthranilates; base-mediated cyclization, benzoyl migration, sulfene

Introduction

As part of our on-going research program aimed at identifying new anti-HCV agents,[1] we were interested in synthesizing 1-benzoyl-6-(2-bromophenoxy)-1*H*-2,1-benzothiazin-4(3*H*)-one 2,2-dioxide derivative **1** (Scheme 1).

The 1*H*-2,1-benzothiazin-4(3*H*)-one 2,2-dioxide nucleus has been definitely less explored, both in terms of chemical space[2] and biological relevance, with respect to its positional isomer 2*H*-1,2-benzothiazin-4(3*H*)-one 2,2-dioxide, whose scaffold characterizes very successful compounds such as the non-steroidal anti-inflammatory "oxicams".

The synthetic route to obtain the 1*H*-2,1-benzothiazine-4(3*H*)-one 2,2-dioxide skeleton was first reported simultaneously by two different groups, Loev and co-workers[3] and Rossi and co-workers.[4] Both groups described a virtually identical five-step procedure which entails: (1) the conversion of sulfoacetic acid into its carboxylic methyl half-ester and then (2) into the sulfonylchloride which was then (3) reacted with aniline to give methyl *N*-phenylsulfamoylacetate;

followed (4) by hydrolysis of this ester-amide and (5) cyclization with PPA. An improved 3-step synthesis was then developed by Lombardino which entails the base-mediated cyclization of a *N*-alkyl-*N*-(methylsulfonyl)anthranilate, prepared from the coupling of an anthranilate and methanesulfonyl chloride (MsCl), followed by *N*-alkylation of the resulting sulfonamide.[5] This general method results in a relatively high overall yield and offers an easier entry into the 2,1-benzothiazine 2,2-dioxide heterocyclic system. It must be pointed out that the cyclization only occurs for the *N*-alkylated intermediates since the presence of a strongly acidic sulfonamide hydrogen prevents further formation of the methyl carbanion that is essential for the cyclization reaction.[6]

More recently, a solid-phase method for the synthesis of 1*H*-2,1-benzothiazine-4(3*H*)-one 2,2-dioxide derivatives utilizing polymer-bound anthranilic acid derivatives was reported by Jeon and co-workers.[7] This procedure is suitable for the combinatorial generation of drug-like heterocyclic compound libraries even though it is not associated with high yields of the target compounds.

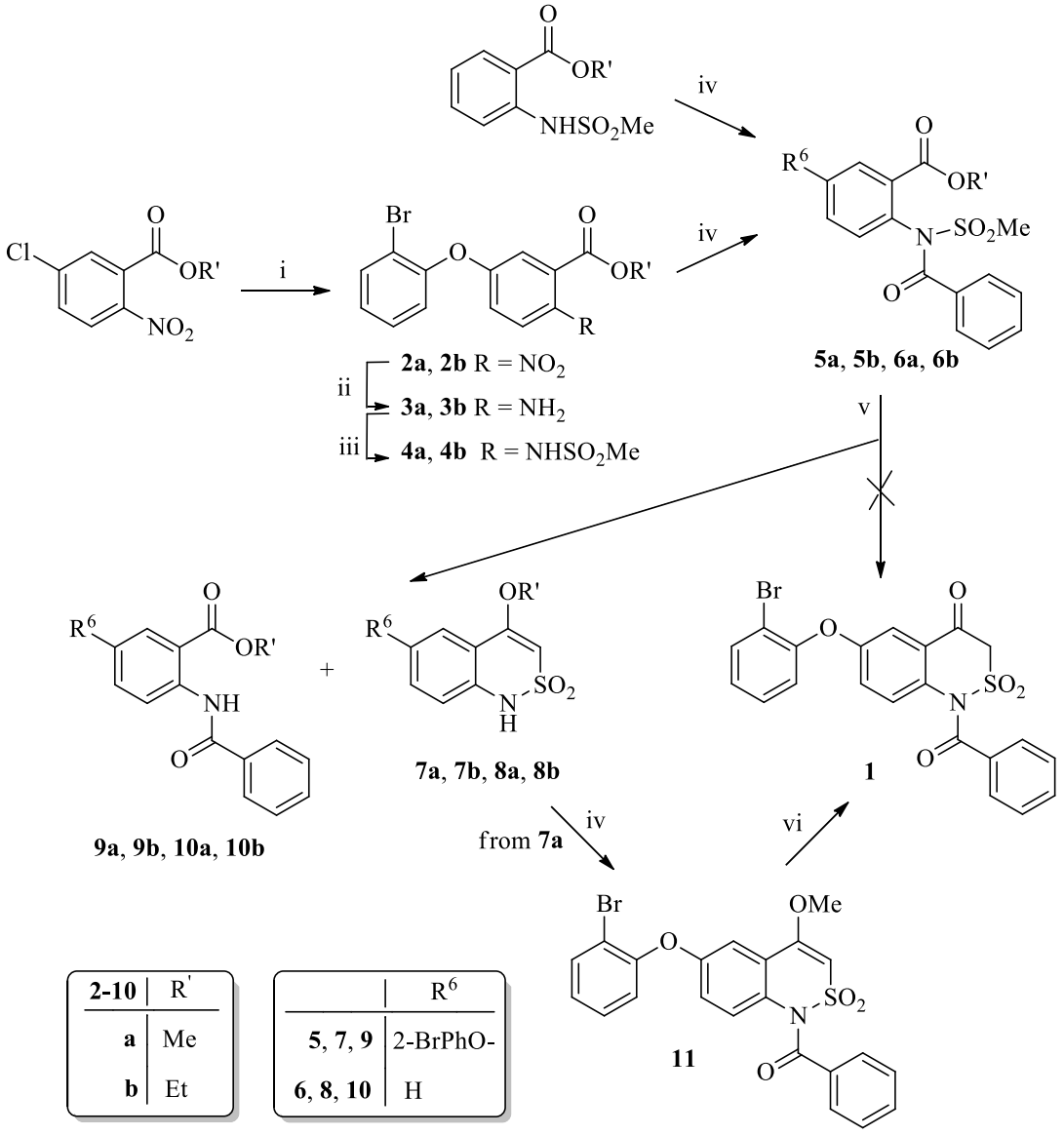
Results and Discussion

The more convenient Lombardino procedure was chosen to obtain compound **1**. Actually, through a serendipitous discovery we found an interesting way to synthesize 4-alkoxy-1*H*-2,1-benzothiazine 2,2-dioxide derivatives.

Thus, as depicted in Scheme 1, the *N*-sulfonylanthranilate **4a** was prepared by the reaction of methyl 5-chloro-2-nitrobenzoate[8] with 2-bromophenol, in DMSO and in the presence of K_2CO_3, followed by the catalytic reduction to amino derivative **3a**[9] and treatment with MsCl in pyridine and CH_2Cl_2. The reaction of *N*-(methylsulfonyl)anthranilate **4a** with benzoyl chloride and NaH in dry THF gave the *N*-benzoyl-*N*-(methylsulfonyl)anthranilate **5a**. When this key intermediate **5a** was submitted to the cyclization step by treatment with NaH in dry DMF, the desired cyclization product **1** was not obtained while 6-(2-bromophenoxy)-4-methoxy-1*H*-2,1-benzothiazine 2,2-dioxide **7a** was formed as the major reaction product (40% yield) together with *N*-benzoylanthranilate **9a** (20% yield). The formation of these products is really unusual and contrasts what has already been reported in literature; indeed the cyclization of *N*-alkyl-*N*-(methylsulfonyl)anthranilates under basic conditions usually gives the 4-keto 2,1-benzothiazines and not the 4-alkoxy derivatives.[5, 2b]

The structure of 4-methoxy derivative **7a** was assigned only by NMR experiments since it was not possible to obtain this compound in a suitable crystal form for X-ray analysis. Its ^{1}H NMR spectrum shows the MeO and H-3 signals as singlets at δ 3.79 and δ 6.67, respectively together with a broad singlet at δ 11.44 due to a NH exchangeable proton. Moreover, ^{13}C NMR spectrum indicates two diagnostic signals: a singlet of MeO at 57.25 ppm and a singlet of C-3 at 100.57 ppm. To definitively confirm the exact structure of compound **7a**, a bidimensional NOESY spectrum was performed. The results indicate two main interactions: the first between

the 4-OMe and the H-3 proton and the second between the same OMe group with the H-5 proton (Figure 1).



Scheme 1. Synthetic route. Reagents and conditions: (i) 2-bromophenol, K_2CO_3, DMSO, 100 °C; (ii) H_2, Ni-Raney, EtOAc, r.t., 1 atm; (iii) MsCl, dry pyridine, dry CH_2Cl_2, 0 °C to r.t.; (iv) benzoyl chloride, NaH, dry THF, 0 °C to r.t.; (v) NaH, dry DMF, 0 °C to r.t.; (vi) 48% HBr, 80-90 °C.

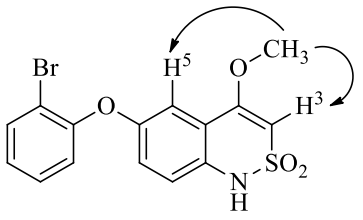


Figure 1. NOESY experiments for **7a** showed two main interactions: 4-OMe→H-3 and 4-OMe→H-5.

Besides the ^{1}H NMR and ^{13}C NMR experiments, the structure of the *N*-benzoylanthranilate **9a** was unambiguously assigned through X –ray crystallography (Figure 2).

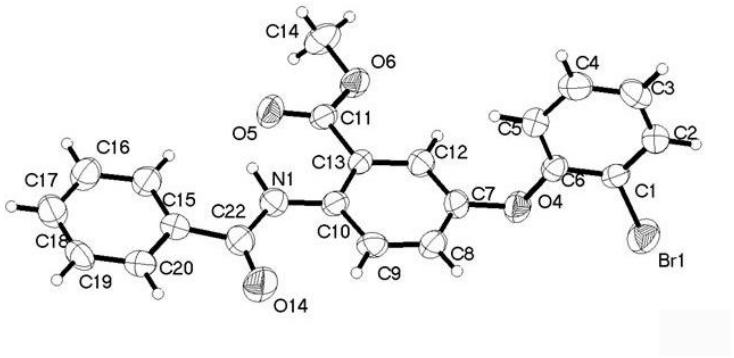


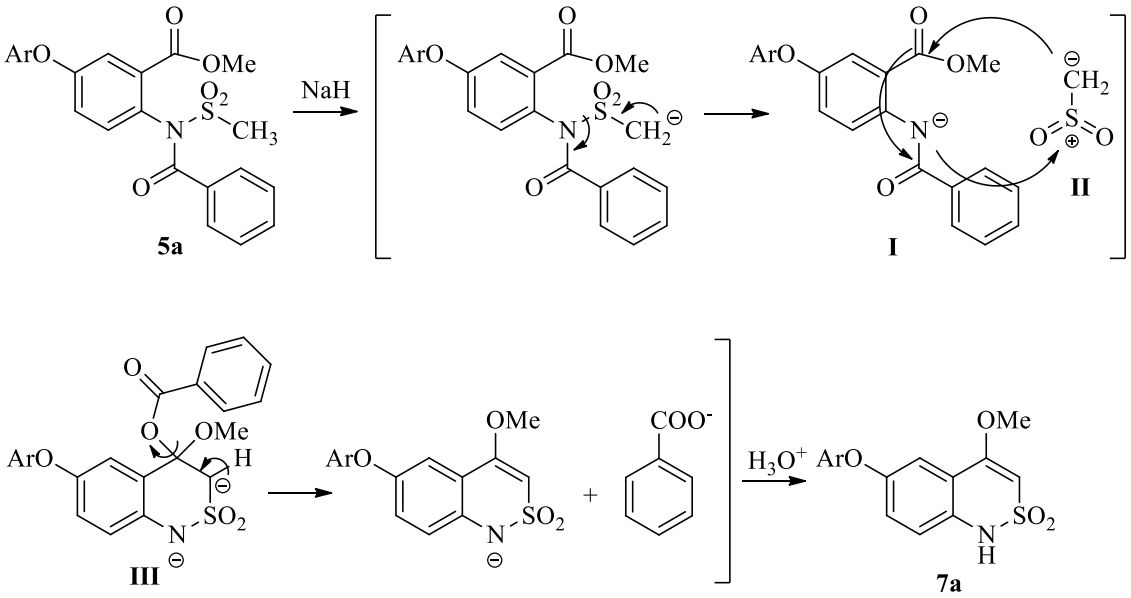
Figure 2. ORTEP drawing of compound **9a**.

The same behaviour was observed when the ethyl ester derivative **5b** was used in the cyclization step; the corresponding 4-ethoxy derivative **7b** was obtained (35% yield) together with *N*-benzoylanthranilate **9b** (25% yield) (Scheme 1). In order to evaluate the reaction reproducibility and to exclude any influence of the 2-bromophenoxy substituent on the reaction trend, the cyclization was repeated using both unsubstituted methyl and ethyl *N*-benzoyl-*N*-(methylsulfonyl)anthranilate, **6a** and **6b** respectively; again 4-alkoxy 2,1-benzothiazines **8a** (36%) and **8b** (33%) were obtained together with *N*-benzoylanthranilate **10a**[10] (20%) and **10b**[11] (25%)**.**

However, to obtain the target compound **1**, 4-alkoxy derivative **7a** was elaborated further by *N*-benzoylation, under basic conditions in THF, to derivative **11** which was subsequently *O*-demethylated in 48% HBr (Scheme 1). The latter reaction was carefully monitored to minimize the *N*-debenzoylation reaction.

Turning back our attention to the cyclization step, the unexpected formation of both 4-alkoxy derivatives **7** and **8** together with *N*-benzoylanthranilates **9** and **10** led us to speculate on the reaction mechanism. In a first hypothesis, it was supposed that desulfonylation occurs together with cyclization on the ester group followed by dehydration. Thus, *N*-benzoylanthranilate **9a** was obtained by desulfonylation. On the other hand, 4-alkoxy-*N*-benzoyl intermediate (*i.e.*, **11**) had to be obtained as a result of cyclization/dehydration. Since 4-methoxy 2,1-benzothiazine **7a** was obtained, only an additional *N*-debenzoylation of 4-alkoxy-*N*-benzoyl intermediate **11** could explain the formation of derivative **7a**. Nevertheless, it must be noted that it has never been reported that cyclization on the ester group is followed by dehydration when the *N*-alkyl-*N*-methylsulfonylanthranilate substrate is used. This observation led us to further speculate that the following mechanism, depicted in Scheme 2 for methyl ester **5a** (Ar = 2-BrPh), might be

operative: under basic cyclization conditions the methylsulfonyl group is removed which generates the sulfene species (**II**)[12] together with **9a** in its anion form (**I**); the highly reactive sulfene (**II**) can react with **I** giving a simultaneous nucleophilic/electrophilic reaction with the methyl ester and with the nitrogen anion, respectively; this makes it possible for the benzoyl to migrate from the nitrogen to the oxygen atom (**III**). The benzoyl migration allows the C-4 position to be occupied by a benzoyloxy group, which is a better leaving group than the methoxy one. The benzoate leaves, via cB1 elimination, permitting the unexpected 6-(2-bromophenoxy)-4-methoxy-1*H*-2,1-benzothiazine 2,2-dioxide **7a** to be obtained. The low yield observed for compound **7a**, and in general for the other 4-alkoxy 2,1-benzothiazines, could be due to the instability of the sulfene species which hampers a quantitative reaction with intermediate **I**; unreacted **I** furnishes benzamide **9a** after acidic workup.



Scheme 2. Postulated reaction mechanism.

Conclusions

In conclusion, a reliable procedure for synthesizing 4-alkoxy-1*H*-2,1-benzothiazines 2,2-dioxide was serendipitously discovered through an unexpected cyclization reaction carried out on *N*-benzoyl-*N*-(methylsulfonyl)anthranilates. Nevertheless, this cyclization step results in a low yield which needs to be improved to have an efficient synthetic method. Despite this limitation, the procedure herein reported is, to the best of our knowledge, the only way to achieve 4-alkoxy-1*H*-2,1-benzothiazines 2,2-dioxide.

These 4-alkoxy derivatives can be further functionalized at the N-1 position to prepare unsymmetrically *N*,*O*-disubstituted 1*H*-2,1-benzothiazine 2,2-dioxide derivatives.

Attempts are currently underway to improve the yields and apply the new methodology to the synthesis of additional analogues.

Experimental Section

General. All starting materials were commercially available, unless otherwise indicated. Reagents and solvents were purchased from common commercial suppliers and were used as such. After extraction, organic layers were collected, dried over anhydrous Na_2SO_4 and the solvents were removed with a Büchi rotary evaporator at reduced pressure. All reactions were routinely checked by thin-layer chromatography (TLC) on silica gel 60F254 (Merck) and visualized by using UV or iodine. Flash column chromatography separations were carried out on Merck silica gel 60 (mesh 230-400). Melting points were determined in capillary tubes (Büchi Electrotermal model 9100) and are uncorrected. ^{1}H NMR spectra were recorded at 400 MHz (Bruker Avance DRX-400) as well as 2D ^{1}H NMR NOESY run in phase sensitive mode. ^{13}C NMR spectra were recorded at 100 MHz (Bruker Avance DRX-400). Spectra were acquired at 298 K and chemical shifts are given in ppm (δ) relative to TMS. Data processing was performed with standard Bruker software XwinNMR and the spectral data are consistent with the assigned structures. HRMS experiments were performed in the positive ion mode using electron spray ionization (ESI) source; the LC−MS machines consist of an HPLC Agilent 1290 Infinity System equipped with a MS detector Agilent 6540UHD Accurate Mass Q-TOF. Elemental analyses were performed on a Fisons elemental analyzer, model EA1108CHN, and data for C, H, and N are within 0.4% of the theoretical values. Yields were of purified product and were not optimized.

Methyl 5-(2-bromophenoxy)-2-nitrobenzoate (2a).[9] A mixture of methyl 5-cloro-2-nitrobenzoate[8] (4.00 g, 18.50 mmol), 2-bromophenol (1.96 mL, 18.50 mmol) and K_2CO_3 (3.84 g, 27.80 mmol) in DMSO (30 mL) was heated at 100 °C for 3 h under stirring. After cooling, the mixture was poured into ice-water and the obtained precipitate was filtered off washing with water to give **2a** as a white solid (6.1 g, 93%) which was used in the next step without further purification; mp 54-55 °C. ^{1}H-NMR (DMSO-d_6) δ 3.83 (s, 3H, OCH_3), 7.20 (dd, 1H, J = 2.8 and 9.1 Hz, H-4), 7.25-7.44 (m, 3H, H-6, H-4' and H-6'), 7.48-7.60 (m, 1H, H-5'), 7.83 (dd, 1H, J = 1.4 and 7.9 Hz, H-3'), 8.16 (d, 1H, J = 9.1 Hz, H-3). ^{13}C NMR ($CDCl_3$) δ 52.80, 117.06, 118.00, 119.01, 124.32, 128.22, 129.00, 130.90, 132.92, 135.94, 143.14, 152.30, 162.60, 166.90. HRMS (ESI) calculated for $C_{14}H_{11}BrNO_5[M + H]^+$ 350.97424, found 350.97486.

Ethyl 5-(2-bromophenoxy)-2-nitrobenzoate (2b) was also prepared with similar results starting from ethyl 5-cloro-2-nitrobenzoate:[13] yield 93%, yellow oil. ^{1}H NMR ($CDCl_3$) δ 1.38 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 4.40 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 7.00 (dd, J = 2.6 and 9.0 Hz, 1H, H-4), 7.09 (d, J = 2.6 Hz, 1H, H-6), 7.15-7.25 (m, 2H, H-4' and H-6'), 7.35-7.40 (m, 1H, H-5'), 7.72 (dd, J = 1.5 and 8.0 Hz, 1H, H-3'), 8.05 (d, J = 9.0 Hz, 1H, H-3). ^{13}C NMR ($CDCl_3$) δ 13.76,

62.74, 116.11, 116.58, 117.69, 122.85, 126.70, 127.52, 129.40, 131.48, 134.44, 141.54, 150.87, 161.16, 165.54. HRMS (ESI) calculated for $C_{15}H_{13}BrNO_5$ $[M + H]^+$ 365.99772, found 365.99717.

Methyl 2-amino-5-(2-bromophenoxy)benzoate (3a).[9] A solution of nitro derivative **2a** (6.10 g, 17.32 mmol) in EtOAc (80 mL) was hydrogenated over catalytic amount of Raney nickel at room temperature and under H_2 flux for 5 h. The mixture was then filtered over Celite and evaporated to dryness under reduced pressure giving aniline derivative **3a** as a yellow oil (3.89 g, 70%) which was used in the next step without further purification. ^{1}H NMR ($CDCl_3$) δ 3.85 (s, 3H, OCH_3), 5.52 (bs, 2H, NH_2), 6.75-6.85 (m, 2H, H-3 and H-6'), 6.87-6.98 (m, 1H, H-4'), 7.05 (dd, *J* = 2.9 and 8.8 Hz, 1H, H-4), 7.15-7.27 (m, 1H, H-5'), 7.54-7.65 (m, 2H, H-6 and H-3'). ^{13}C NMR ($CDCl_3$) δ 50.78, 110.49, 112.08, 116.38, 117.87, 121.03, 122.56, 125.96, 127.95, 132.67, 144.96, 146.32, 154.12, 166.52. HRMS (ESI) calculated for $C_{14}H_{13}BrNO_3[M + H]^+$ 321.00006, found 321.00075.

Ethyl 2-amino-5-(2-bromophenoxy)benzoate (3b) was also prepared with similar results starting from **2b**: yellowish oil, yield 83%. ^{1}H NMR ($CDCl_3$) δ 1.30 (t, *J* = 7.1 Hz, 3H, $OCH_2C\mathit{H}_3$), 4.30 (q, *J* = 7.1 Hz, 2H, $OC\mathit{H}_2CH_3$), 6.70 (d, *J* = 8.8 Hz, 1H, H-3), 6.80 (dd, *J* = 1.4 and 8.2 Hz, 1H, H-6'), 6.80-6.90 (m, 1H, H-4'), 7.05 (dd, *J* = 2.9 and 8.9 Hz, 1H, H-4), 7.15-7.25 (m, 1H, H-5'), 7.55-7.65 (m, 2H, H-3' and H-6). ^{13}C NMR ($CDCl_3$) δ 14.28, 60.64, 111.59, 112.88, 117.43, 118.17, 121.98, 123.60, 126.85, 128.43, 133.67, 145.67, 147.23, 155.29, 167.49. HRMS (ESI) calculated for $C_{15}H_{15}BrNO_3$ $[M + H]^+$ 336.02354, found 336.02324.

Methyl 5-(2-bromophenoxy)-2-[(methylsulfonyl)-amino]benzoate (4a). A solution of MsCl (0.68 mL, 8.74 mmol) in dry CH_2Cl_2 (5 mL) was slowly added under stirring to a solution of methyl anthranilate **3a** (2.56 g, 7.95 mmol) in dry CH_2Cl_2 (10 mL) and dry pyridine (0.71 mL, 8.74 mmol); cooled to 0 °C. After 12 h at room temperature, the reaction mixture was poured into ice-water acidified to pH ~ 6 with 2N HCl and extracted with $CHCl_3$ (3 x 15 mL). The combined organic layers were dried and the solvent was evaporated to dryness. The slurry residue was ground with ice-water to obtain a white solid which was filtered off to give **4a** (2.78 g, 87%) which was used in the next step without further purification; mp 123-125 °C. ^{1}H NMR ($CDCl_3$) δ 3.00 (s, 3H, SO_2CH_3), 3.90 (s, 3H, OCH_3,), 6.90 (dd, *J* = 1.4 and 8.1 Hz, 1H, H-6'), 7.05-7.10 (m, 1H, H-4'), 7.20 (dd, *J* = 2.9 and 9.1 Hz, 1H, H-4), 7.25-7.30 (m, 1H, H-5'), 7.60-7.65 (m, 2H, H-6 and H-3'), 7.75 (d, *J* = 9.1 Hz, 1H, H-3), 10.00 (bs, 1H, NH). ^{13}C NMR ($CDCl_3$) δ 39.88, 52.80, 114.82, 117.13, 120.39, 120.41, 120.69, 124.77, 125.59, 128.89, 134.09, 136.24, 152.19, 153.13, 167.65. HRMS (ESI) calculated for $C_{15}H_{15}BrNO_5S$ $[M + H]^+$ 399.98544, found 399.98504.

Ethyl 5-(2-bromophenoxy)-2-[(methylsulfonyl)amino]benzoate (4b) was also prepared with similar results starting from amino derivative **3b**: yield 65%, white solid; mp 117-119 °C. ^{1}H NMR ($CDCl_3$) δ 1.40 (t, *J* = 7.1 Hz, 3H, $OCH_2C\mathit{H}_3$), 3.05 (s, 3H, SO_2CH_3), 4.40 (q, *J* = 7.1 Hz, 2H, $OC\mathit{H}_2CH_3$), 6.95 (dd, 1H, *J* = 1.1 and 8.1, H-6'), 7.05-7.10 (m, 1H, H-4'), 7.15 (dd, *J* = 3.0 and 9.0 Hz, 1H, H-4), 7.25-7.35 (m, 1H, H-5'), 7.65 (dd, *J* = 1.3 and 8.0 Hz, 1H, H-3'), 7.70-7.75 (m, *2*H, H-3 and H-6), 10.20 (bs, 1H, NH). ^{13}C NMR ($CDCl_3$) δ 14.09, 39.86, 62.07,

114.65, 117.50, 120.12, 120.62, 120.81, 124.54, 125.47, 128.85, 134.06, 136.31, 152.02, 153.24, 167.21. HRMS (ESI) calculated for $C_{16}H_{17}BrNO_5S$ $[M + H]^+$ 414.00109, found 414.00063.

Methyl 2-[benzoyl(methylsulfonyl)amino]-5-(2-bromophenoxy)benzoate (5a). A solution of **4a** (1.16 g, 2.90 mmol) in dry THF (10 mL), was added to a stirred suspension of 60% NaH (0.174 g, 4.35 mmol) in dry THF (5 mL), cooled to 0 °C. After 5 min, a solution of benzoyl chloride (0.51 mL, 4.35 mmol) in dry THF (5 mL) was slowly added. The mixture was stirred at room temperature for 24 h, then poured into ice-water and acidified to pH ~5 with 2N HCl. The resultant solid was filtered off, dried and purified by flash column chromatography on silica gel eluting with cyclohexane/EtOAc (9:1) to give intermediate **5a** (1.05 g, 72%) as whitish solid; mp 144-145 °C. ^{1}H NMR ($CDCl_3$) δ 3.60 (s, 3H, SO_2CH_3), 3.85 (s, 3H, OCH_3), 6.90-7.10 (m, 2H, Ar-H), 7.05-7.15 (m, 1H, H-4'), 7.15-7.25 (m, 2H, Ar-H), 7.30-7.45 (m, 6H, Ar-H), 7.65 (dd, *J* = 1.9 and 8.0 Hz, 1H, H-3'). ^{13}C NMR ($CDCl_3$) δ 42.27, 52.61, 115.52, 119.78, 120.95, 121.92, 126.54, 127.91, 128.65, 129.08, 129.89, 130.82, 131.33, 133.71, 134.24, 134.78, 151.85, 157.36, 164.92, 169.93. HRMS (ESI) calculated for $C_{22}H_{19}BrNO_6S$ $[M + H]^+$ 504.01165, found 504.01046.

Ethyl 2-[benzoyl(methylsulfonyl)amino]-5-(2-bromophenoxy)benzoate (5b) was also prepared with similar results starting from derivative **4b**: yield 91%, white solid; mp 104-109 °C. ^{1}H NMR ($CDCl_3$) δ 1.25 (t, *J* = 7.1 Hz, 3H, $OCH_2C\mathit{H}_3$), 3.60 (s, 3H, SO_2CH_3), 4.25 (q, *J* = 7.1 Hz, 2H, $OC\mathit{H}_2CH_3$), 6.90-7.10 (m, 2H, Ar-H), 7.05-7.15 (m, 1H, H-4'), 7.15-7.25 (m, 2H, Ar-H), 7.27-7.40 (m, 5H, Ar-H), 7.45 (d, *J* = 2.0 Hz, 1H, H-6), 7.65 (m, 1H, H-3'). ^{13}C NMR ($CDCl_3$) δ 14.09, 42.28, 61.86, 115.43, 120.13, 120.65, 121.76, 126.46, 127.89, 128.72, 129.05, 130.28, 130.86, 131.30, 133.72, 134.22, 134.70. HRMS (ESI) calculated for $C_{23}H_{21}BrNO_6S$ $[M + H]^+$ 518.02730, found 518.02608.

Methyl 2-[benzoyl(methylsulfonyl)amino]benzoate (6a) was also prepared with similar results starting from methyl 2-[(methylsulfonyl)amino]benzoate:[5a] yield 75%, white solid; mp 138-140 °C. ^{1}H NMR ($CDCl_3$) δ 3.65 (s, 3H, SO_2CH_3), 3.90 (s, 3H, OCH_3), 7.10-7.20 (m, 2H, Ar-H), 7.25-7.30 (m, 1H, Ar-H), 7.30-7.40 (m, 3H, Ar-H), 7.40-7.55 (m, 2H, Ar-H), 7.85 (dd, *J* = 1.4 and 7.8 Hz, 1H, H-6). ^{13}C NMR ($CDCl_3$) δ 42.33, 52.44, 127.84, 128.61, 128.66, 129.37, 131.27, 131.46, 132.88, 133.33, 133.76, 136.33, 165.49, 169.88. HRMS (ESI) calculated for $C_{16}H_{16}NO_5S$ $[M + H]^+$ 334.07492, found 334.07466.

Ethyl 2-[benzoyl(methylsulfonyl)amino]benzoate (6b) was also prepared with similar results starting from ethyl 2-[(methylsulfonyl)amino]benzoate:[14] yield 50%, white solid; mp 135-138 °C. ^{1}H NMR ($CDCl_3$) δ 1.27 (t, *J* = 7.1 Hz, 3H, $OCH_2\mathit{CH}_3$), 3.60 (s, 3H, SO_2CH_3), 4.15 (q, *J* = 7.1 Hz, 2H, $O\mathit{CH}_2CH_3$), 7.15-7.20 (m, 2H, Ar-H), 7.25-7.35 (m, 1H, Ar-H), 7.37-7.45 (m, 3H, Ar-H), 7.45-7.55 (m, 2H, Ar-H), 7.80 (dd, *J* = 1.5 and 7.8 Hz, 1H, H-6). ^{13}C NMR ($CDCl_3$) δ 14.12, 42.34, 61.61, 127.80, 128.67, 129.00, 129.33, 131.22, 131.41, 132.73, 133.28, 133.80, 136.33, 165.07, 169.85. HRMS (ESI) calculated for $C_{17}H_{18}NO_5S$ $[M + H]^+$ 348.09057, found 348.09009.

6-(2-Bromophenoxy)-4-methoxy-1*H*-2,1-benzothiazine 2,2-dioxide (7a) and methyl (2-benzamido)-5-(2-bromophenoxy)benzoate (9a). A solution of compound **5a** (0.35 g, 0.68 mmol) in dry DMF (6 mL) was added dropwise to a suspension of 60% NaH (0.082 g, 2.04 mmol) in dry DMF (4 mL), cooled at 0 °C. The reaction mixture was allowed to reach room temperature, stirred for 6 h, then poured into ice-water and acidified to pH ~5 with 2N HCl. The precipitate formed was collected by filtration, dried and purified by flash column chromatography on silica gel, eluting with cyclohexane/EtOAc (6:4). to give compound **9a** (Rf>) (0.06 g, 20%), as a pale yellowish solid, followed by compound **7a** (Rf<) (0.10 g, 40%) as a white solid.

Compound (7a). Mp 175-177 °C. ^{1}H NMR (DMSO-*d*$_6$) δ 3.79 (s, 3H, OCH_3), 6.67 (s, 1H, H-3), 7.05 (dd, *J* = 1.4 and 8.1 Hz, 1H, H-6'), 7.10-7.17 (m, 2H, H-8 and H-4'), 7.18 (d, *J* = 2.8 Hz, 1H, H-5), 7.22 (dd, *J* = 2.8 and 8.7 Hz, 1H, H-7), 7.35-7.42 (m, 1H, H-5'), 7.73 (dd, *J* = 1.5 and 8.0 Hz, 1H, H-3'), 11.44 (bs, 1H, NH). ^{13}C NMR (DMSO-*d*$_6$) δ 57.25, 100.57, 112.81, 114.29, 117.40, 119.83, 121.08, 122.76, 126.31, 130.02, 133.53, 134.27, 151.45, 153.37, 157.97. 2D ^{1}H NMR NOESY spectra showed two relevant NOE cross-peaks: 4-OCH_3→H-3; 4-OCH_3→H-5. HRMS (ESI) calculated for $C_{15}H_{13}BrNO_4S$ $[M + H]^+$ 381.97487, found 381.97418. Anal. Calcd (%) for $C_{15}H_{12}BrNO_4S$: C, 47.13; H, 3.16; N, 3.66. Found: C, 47.22; H, 3.18 ; N, 3.67.

Compound (9a). Mp 108-111 °C. ^{1}H NMR (DMSO-*d*$_6$) δ 3.83 (s, 3H, OCH_3), 7.12-7.21 (m, 2H, H-4' and H-6'), 7.36 (dd, *J* = 3.0 and 9.1 Hz, 1H, H-4), 7.41-7.46 (m, 2H, H-6 and H-5'), 7.57-7.66 (m, 3H, H-3", H-4" and H-5"), 7.77 (dd, *J* = 1.2 and 8.0 Hz, 1H, H-3'), 7.94-7.97 (m, 2H, H-2" and H-6"), 8.49 (d, *J* = 9.1 Hz, 1H, H-3), 11.37 (bs, 1H, NH). ^{13}C NMR (DMSO-*d*$_6$) δ 53.25, 114.59, 119.02, 119.83, 121.54, 123.88, 124.11, 126.69, 127.53, 129.38, 130.11, 132.61, 134.38, 134.73, 136.17, 152.16, 152.91, 165.15, 167.53. HRMS (ESI) calculated for $C_{21}H_{17}BrNO_4$ $[M + H]^+$ 426.03410, found 426.03294. Anal. Calcd (%) for $C_{21}H_{16}BrNO_4$: C, 59.17; H, 3.78; N, 3.29. Found: C, 59.57, H, 4.17; N, 3.28.

6-(2-Bromophenoxy)-4-ethoxy-1*H*-2,1-benzothiazine 2,2-dioxide (7b) and ethyl (2-benzamido)-5-(2-bromophenoxy)benzoate (9b). The title compounds were obtained in a manner similar to that used to synthesize compounds **7a** and **9a**, starting from **5b** instead of **5a**.

Compound (7b). Yield 35%, white solid; mp 153-156 °C. ^{1}H NMR (DMSO-*d*$_6$) δ 1.32 (t, *J* = 7.0 Hz, 3H, $OCH_2C\mathit{H}_3$), 4.03 (q, *J* = 7.0 Hz, 2H, $OC\mathit{H}_2CH_3$), 6.64 (s, 1H, H-3), 7.00 (dd, *J* = 1.4 and 8.1 Hz, 1H, H-6'), 7.05-7.20 (m, 3H, H-7, H-8 and H-4'), 7.29 (d, *J* = 2.8 Hz, 1H, H-5), 7.32-7.42 (m, 1H, H-5'), 7.74 (dd, *J* = 1.6 and 8.0 Hz, 1H, H-3'), 11.43 (bs, 1H, NH). ^{13}C NMR (DMSO-*d*$_6$) δ 14.28, 65.49, 100.78, 113.63, 113.96, 117.61, 119.77, 120.50, 122.71, 126.00, 129.94, 133.70, 134.23, 151.12, 153.58, 156.95. HRMS (ESI) calculated for $C_{16}H_{15}BrNO_4S$ $[M + H]^+$ 395.99052, found 395.98987. Anal. Calcd (%) for $C_{16}H_{14}BrNO_4S$: C, 48.50; H, 3.56; N, 3.53. Found: C, 48.87; H, 3.90; N, 3.23.

Compound (9b). Yield 25%, yellowish solid; mp 140-143 °C. ^{1}H NMR (DMSO-*d*$_6$) δ 1.20 (t, *J* = 7.10 Hz, 3H, $OCH_2\mathit{CH}_3$), 4.25 (q, *J* = 7.10 Hz, 2H, $O\mathit{CH}_2CH_3$), 7.05-7.22 (m, 2H, H-4' and H-6'), 7.24-7.48 (m, 3H, H-4, H-6 and H-5'), 7.50-7.65 (m, 3H, H-3", H-4" and H-5"), 7.74 (d, *J* = 8.0 Hz, 1H, H-3'), 7.85-8.00 (m, 2H, H-2" and H-6"), 8.40 (d, *J* = 8.9 Hz, 1H, H-3), 11.29 (bs,

1H, NH). ^{13}C NMR (DMSO-d_6) δ 14.30, 62.05, 114.46, 119.42, 120.50, 121.29, 123.87, 124.08, 126.57, 127.56, 129.35, 130.08, 132.60, 134.35, 134.72, 136.04, 152.10, 153.00, 165.18, 167.08. HRMS (ESI) calculated for $C_{22}H_{19}BrNO_4$ $[M + H]^+$ 440.04975, found 440.04872. Anal. Calcd (%) for $C_{22}H_{18}BrNO_4$: C, 60.01; H, 4.12; N, 3.18. Found: C, 59.63; H, 3.75; N, 3.56.

4-Methoxy-1*H*-2,1-benzothiazine 2,2-dioxide 8a and methyl (2-benzamido)benzoate (10a). The title compounds were obtained in manner similar to that used to synthesize compounds **7a** and **9a**, starting from **6a** instead of **5a**.

Compound (8a). yield 36%, grey solid; mp 158-161 °C. ^{1}H NMR (DMSO-d_6) δ 3.85 (s, 3H, OCH_3), 6.60 (s, 1H, H-3), 7.00-7.20 (m, 2H, H-7 and H-8), 7.40-7.55 (m, 1H, H-6), 7.80 (d, J = 7.8 Hz, 1H, H-5), 11.40 (bs, 1H, NH). ^{13}C NMR (DMSO-d_6) δ 57.13, 99.74, 116.30, 117.59, 122.33, 124.67, 132.16, 137.54, 158.70. HRMS (ESI) calculated for $C_9H_{10}NO_3S$ $[M + H]^+$ 212.03814, found 212.03805. Anal. Calcd (%) for $C_9H_9NO_3S$: C, 51.17; H, 4.29; N, 6.63. Found C, 51.19; H, 4.31; N, 6.60.

Compound (10a). yield 20%, yellowish solid; mp 97-99 °C (lit.,[10] mp 97-98 °C). ^{1}H NMR (DMSO-d_6) δ 3.90 (s, 3H, OCH_3), 7.22 (t, J = 8.0 Hz, 1H, H-5), 7.55-7.75 (m, 4H, Ar-H), 7.90-7.95 (m, 2H, Ar-H), 8.05 (dd, J = 1.4 and 7.9 Hz, 1H, H-3), 8.60 (d, J = 8.3 Hz, 1H, H-6), 11.30 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ 53.12, 117.48, 121.23, 123.83, 127.51, 129.44, 131.18, 132.68, 134.80, 134.82, 140.73, 165.24, 168.53. HRMS (ESI) calculated for $C_{15}H_{14}NO_3$ $[M + H]^+$ 256.09737, found 256.09695. Anal. Calcd (%) for $C_{15}H_{13}NO_3$: C, 70.58; H, 5.13; N, 5.49. Found: C, 70.18; H, 4.73; N, 5.19.

4-Ethoxy-1*H*-2,1-benzothiazine 2,2-dioxide 8b and ethyl (2-benzamido)benzoate (10b). The title compounds were obtained in a manner similar to that used to synthesize compounds **7a** and **9a**, starting from **6b** instead of **5a**.

Compound (8b). yield 33%, yellowish solid; mp 150-152 °C. ^{1}H NMR (DMSO-d_6) δ 1.39 (t, J = 7.1 Hz, 3H, $OCH_2\mathit{CH_3}$), 4.15 (q, J = 7.1 Hz, 2H, $O\mathit{CH_2}CH_3$), 6.65 (s, 1H, H-3), 7.10-7.20 (m, 2H, H-7 and H-8), 7.45 (t, J = 7.5 Hz, 1H, H-6), 7.75 (d, J = 7.5 Hz, 1H, H-5), 11.30 (bs, 1H, NH). ^{13}C NMR (DMSO-d_6) 14.40, 65.32, 99.95, 116.24, 117.59, 122.28, 124.74, 132.10, 137.61, 157.72. HRMS (ESI) calculated for $C_{10}H_{12}NO_3S$ $[M + H]^+$ 226.05379, found 226.05333. Anal. Calcd (%) for $C_{10}H_{11}NO_3S$: C, 53.32; H, 4.92; N, 6.22. Found: C, 53.62; H, 5.22; N, 6.00.

Compound (10b). yield 25%, yellowish solid; mp 95-98 °C (lit.,[11] mp 99 °C). ^{1}H NMR (DMSO-d_6) δ 1.30 (t, J = 7.1 Hz, 3H, $OCH_2\mathit{CH_3}$), 4.30 (q, J = 7.1 Hz, 2H, $O\mathit{CH_2}CH_3$), 7.25 (t, J = 8.0 Hz, 1H, H-5), 7.50-7.75 (m, 4H, H-4, H-3', H-4', and H-5'), 7.90-8.10 (m, 3H, H-3, H-2', and H-6'), 8.55 (d, J = 8.0 Hz, 1H, H-6), 11.50 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ 14.40, 61.86, 117.83, 121.31, 123.83, 127.53, 129.42, 131.18, 132.67, 134.72, 134.82, 140.68, 165.25, 168.00. HRMS (ESI) calculated for $C_{16}H_{16}NO_3$ $[M + H]^+$ 270.11302, found 270.11278. Anal. Calcd (%) for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.62; H, 6.01; N, 4.96.

1-Benzoyl-6-(2-Bromophenoxy)-4-methoxy-1*H*-2,1-benzothiazine 2,2-dioxide (11). Compound **7a** was reacted with benzoyl chloride, using the same procedure as that used to prepare derivative **5a**, to give **11**: yield 67%, a white solid; mp 218-221 °C. ^{1}H NMR ($CDCl_3$) δ 3.90 (s, 3H, CH_3), 6.05 (s, 1H, H-3), 7.15 (m, 3H, Ar-H), 7.20 (d, J = 9 Hz, 1H, H-8), 7.30-7.35

(m, 1H, H-5'), 7.45-7.55 (m, 3H, Ar-H), 7.60-7.70 (m, 2H, Ar-H), 7.90-7.95 (m, 2H, H-2" and H-6"). ^{13}C NMR ($CDCl_3$) δ 56.67, 101.39, 113.59, 115.37, 121.23, 121.36, 124.02, 126.03, 127.32, 128.49, 128.98, 130.32, 131.20, 133.77, 134.11, 134.94, 152.59, 155.60, 160.09, 169.27. HRMS (ESI) calculated for $C_{22}H_{17}BrNO_5S$ $[M + H]^+$ 486.00109, found 486.00021.

1-Benzoyl-6-(2-bromophenoxy)-1*H*-2,1-benzothiazin-4-(3*H*)-one 2,2-dioxide (1). A mixture of benzoyl derivative **11** (0.16 g, 0.33 mmol) and 48% HBr (5 mL) was heated at 80-90 °C until the starting material disappeared. After 6 h, the reaction mixture was cooled and the obtained solid was filtered off and crystallized from EtOH/DMF to give **1** (0.05 g, 32%) as a white solid; mp 181-183 °C. ^{1}H NMR ($CDCl_3$) δ 4.89 (s, 2H, CH_2), 7.05-7.20 (m, 3H, H-8, H-4' and H-6'), 7.27 (dd, *J* = 3.0 and 9.0 Hz, 1H, H-7), 7.30-7.35 (m, 1H, H-5'), 7.50-7.55 (m, 2H, H-3" and H-5"), 7.62 (d, *J* = 3.0 Hz, 1H, H-5), 7.65-7.75 (m, 2H, H-3' and H-4"), 8.00-8.10 (m, 2H, H-2" and H-6"). ^{13}C NMR ($CDCl_3$) δ 61.50, 115.48, 115.78, 122.06, 125.61, 126.73, 127.45, 127.79, 128.77, 129.19, 130.91, 134.29, 134.43, 134.75, 136.09, 151.85, 156.54, 170.99, 183.40. HRMS (ESI) calculated for $C_{21}H_{15}BrNO_5S$ $[M + H]^+$ 471.98544, found 471.98507. Anal. Calcd (%) for $C_{21}H_{14}BrNO_5S$: C, 53.40; H, 2.99; N, 2.97. Found: C, 53.76; H, 3.15; N, 2.58.

Crystal structure analysis

Single crystal diffraction data collection for **9a** was carried out on an XCALIBUR Oxford Instruments diffractometer equipped with a CCD detector, using graphite monochromated MoKα radiation and operating at 50 kV and 30 mA. To maximize the reciprocal space coverage, a combination of ω and φ scans was used, with a step size of 0.5 ° and a time of 15 s/frame. Data were corrected for absorption using the SADABS program.[15] The structure was solved by direct methods (SIR 97 program)[16] and refined by full-matrix least-squares against F2 using all the data, (SHELXTL software package).[17] Non-H atoms were refined anisotropically; H atoms were placed in calculated positions. Atomic coordinates, bond lengths and angles and thermal parameters have been deposited with the Cambridge Crystallographic Database Service, reference number CCDC 773696. Crystal data for **7a**: $C_{21}H_{16}BrNO_4$, FW = 426.26, Monoclinic, space group C2/c (no. 4), *Z* =4, *a* = 17.973(5), *b*= 9.309(3), *c* = 22.112(7) Å, *β* = 92.440(2)°, V = 3696(2) Å^3, ρ_{calc} = 1.53 g.cm^{-3}, λ(Mo-*K*α) = 0.71069 Å, *F*(000) = 1728; 3175 data ($2\theta_{max}$ = 50°) of which 1561 unique, R_{int} = 0.109; 242 parameters, wR_2 = 0.086, *S* = 0.830 (all data), R_1 (with I > 2σ(I)) = 0.041, largest final difference peak/hole +0.464/-0.364 e·Å^{-3}.

Acknowledgements

The authors are grateful to Prof. Francesca Marini for her fruitful discussion and to Prof. Claudio Santi for his help in NOESY experiments. Roberto Bianconi is also gratefully acknowledged for his excellent technical assistance.

References

1. Manfroni, G.; Meschini, F.; Maga, G.; Tabarrini, O.; Sabatini, S.; Cruciani, G.; Cecchetti, V. XIX National Meeting on Medicinal Chemistry. Verona, Italy, September 14-18, **2008**, P-039.
2. For reviews on the chemistry of 2,1-benzothiazines, see: (a) Hong, X.; Harmata, M. in *Progress in Hetrocyclic Chemistry*; Gribble, G. W. and Joule, J. A., Eds: Elesvier: Oxford, 2008; Vol 19, p 1. (b) Lombardino, J. G.; Kuhla, D. E. *Adv. Heterocycl. Chem.* **1981**, *28*, 73.
3. Loev, B.; Kormendy, M. F.; Sander, K. M. *J. Org. Chem*. **1966**, *31*, 3531.
4. Rossi, S.; Pagani, G. *Annali di Chimica* (Rome, Italy) **1966**, *56*, 741; *Chem. Abstr*. **1966**, *65*, 56793.
5. (a) Lombardino, J. G. *J. Heterocyclic Chem*. **1972**, *9*, 315. (b) Lombardino, J. G. *Org. Prep. Poced. Int*. **1971**, *3*, 33.
6. Rossi, S.; Pagani, G. *Annali di Chimica* (Rome, Italy) **1966**, *56*, 728; *Chem. Abstr*. **1966**, *65*, 56792.
7. Jeon, M-K.; Kwon, J-J.; Gong, Y-D.; Lee, D-H. *Tetrahedron* **2008**, *64*, 9060.
8. Naffziger, M. R.; Ashburn, B. O.; Perkins, J. R.; Carter, R. G. *J. Org. Chem.* **2007**, *72*, 9857.
9. Beaulieu, P.; Bonneau, P.; Coulombe, R.; Forgione, P.; Gillard, J.; Jakalian, A.; Rancourt, J. PCT Int. Appl., 037210, 2010; *Chem. Abstr*. **2010**, *152*, 453932.
10. Yin, J.; Buchwald S. L. *Org. Lett*. **2000**, *2*, 1101.
11. Higashino, T.; Kokubo, H.; Goto, A.; Takemoto, M.; Hayashi, E. *Chem. Pharm. Bull*. **1984**, *32*, 3690.
12. King, J. F. *Acc. Chem. Res.* **1975**, *8*, 10.
13. Eto, N.; Nagao, R.; Miyazaki, T. PCT Int. Appl. 085382, 2004; *Chem Abstr*. **2004**, *141*, 331920.
14. Larsen, A. A. U.S. Patent 3 067 237, 1962; *Chem. Abstr*. **1963**, *58*, 27061.
15. Sheldrick, G. M. Program for Empirical Absorption Correction of Area Detector Data. University of Göttingen. Germany, 1996.
16. Altomare, A.; Burla, M. C.; Camalli, M.; Cascarano, G. L.; Giacovazzo, C.; Guagliardi, A.; Moliterni, A. G. G.; Polidori, G.; Spagna, R. *J. Appl. Crystallogr*. **1999**, *32*, 115.
17. Sheldrick, G. M. "SHELXL-97, Program for refinement of crystal structures", University of Göttingen, Göttingen Germany, 1997.

