

# Stereoselective One-Pot Synthesis of Substituted (4Z)-2-Alkyl-4-benzylidene-4H-1,3-benzothiazines<sup>†</sup>

Antonio Herrera,<sup>‡</sup> Roberto Martínez-Alvarez,<sup>\*,‡</sup>  
Pedro Ramiro,<sup>‡</sup> Angel Sánchez,<sup>§</sup> and Rosario Torres<sup>||</sup>

Departamento de Química Orgánica, Facultad de Ciencias Químicas, Universidad Complutense, E-28040 Madrid, Spain, CAI de Resonancia Magnética Nuclear, Facultad de Ciencias Químicas, Universidad Complutense, E-28040 Madrid, Spain, and Laboratorio de Difracción de Rayos X, Facultad de Ciencias Químicas, Universidad Complutense, E-28040 Madrid, Spain

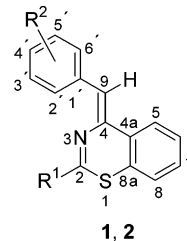
rma@quim.ucm.es

Received February 9, 2004

**Abstract:** Substituted (4Z)-4-benzylidene-2-methyl-4H-1,3-benzothiazines (**1**) and (4Z)-2-ethyl-4-benzylidene-4H-1,3-benzothiazines (**2**) were synthesized by direct stereoselective reactions of *S*-phenyl ethanethioate or *S*-phenyl propanethioate with substituted benzyl nitriles in the presence of triflic anhydride.

Since they were first reported in 1947, benzothiazines have attracted significant interest for their interesting pharmacological properties.<sup>1–7</sup> The synthetic and biological chemistry of the 3,1-benzothiazine nucleus is a relatively unexplored class of compounds from the standpoint of both synthetic chemistry and biological chemistry.<sup>8</sup> Other benzothiazines rings such as 1,2-, 2,1-, 1,4-, and 1,3- have been extensively studied. In particular, 1,3-benzothiazines are of significant interest. Thus, triazolo-1,3-benzothiazines were evaluated for their ability to displace (3*H*)-funitresepam from bovine brain membranes while IDPH-791, an analogue of triazolobenzothiazine, is a well-known centrally acting muscle relaxant.<sup>9</sup> Benzothiazines bearing a nitrooxyethyl group show anti-ischemic properties for heart diseases and for control

## CHART 1. Substituted (4Z)-2-Alkyl-4-benzylidene-4H-1,3-benzothiazines **1** (R<sup>1</sup> = CH<sub>3</sub>) and **2** (R<sup>1</sup> = CH<sub>2</sub>CH<sub>3</sub>) and Their Numbering System



of hypertension.<sup>10</sup> 2-Heterocyclyl-1,3-benzothiazine derivatives are inhibitors of apoptosis and are cytoprotective agents (Chart 1).<sup>11</sup>

Synthetic approaches to 4H-1,3-benzothiazine derivatives include ring-closure reactions of substituted *N*-(3,4-dialkoxyphenylthiomethyl)-2-substituted benzamides with phosphoryl chloride, to yield derivatives of 1,3-benzothiazines<sup>12,13</sup> (Scheme S1, Supporting Information). Treatment of thiosalicylic acid with nitrooxyethylamine nitrate produces 1,3-benzothiazine-2,4-dione derivatives<sup>8</sup> (Scheme S2, Supporting Information). The reaction of benzothiete with tosyl nitrile affords derivatives of the 4H-1,3-benzothiazine through a hetero-Diels–Alder [8 + 2] cycloaddition<sup>14</sup> (Scheme S3, Supporting Information). Pyrrolo-[1,3]benzothiazines can be prepared by intramolecular  $\alpha$ -amidoalkylation cyclizations with internal sulfur atom as nucleophile from *o*-(benzylthio)benzyl alcohol<sup>15</sup> (Scheme S4, Supporting Information). The photocyclization of 1,2,4-triazole-3-thiones leads to triazolo-4H-1,3-benzothiazines<sup>9</sup> (Scheme S5, Supporting Information).

Only a few examples of non-multistep reactions are reported for the preparation of benzothiazine derivatives from easily available starting materials. Among these, we find the dilithiation of thiophenols and subsequent reaction with *N,N*-bis[(benzotriazol-1-yl)methyl]amines<sup>16</sup> (Scheme S6, Supporting Information) and the treatment of thiosalicylic acid with ethyl chloroformate and benzylamine<sup>17</sup> (Scheme S7, Supporting Information).

The reaction of ketones with aliphatic and aromatic nitriles in the presence of triflic anhydride affords alkyl- and arylpyrimidines.<sup>18</sup> Application of this reaction to

\* To whom correspondence should be addressed. Tel: 34 913944325. Fax: 34 913944103.

<sup>†</sup> This work is dedicated to the memory of Dr. J. C. del Amo Aguado, victim of the terrorism on March 11, 2004.

<sup>‡</sup> Departamento de Química Orgánica.

<sup>§</sup> CAI de Resonancia Magnética Nuclear.

<sup>||</sup> Laboratorio de Difracción de Rayos X.

(1) Masaki, M.; Miyake, N.; Tendo, A.; Ishida, M.; Shinozaki, A.; Nomura, Y.; Goto, Y. *WO* 26,959, 1995; *Chem. Abstr.* **1996**, *124*, 146182m.

(2) Levi, S.; Benedini, F.; Bertolini, G.; Dona, G.; Gromo, G.; Sala, A. *WO* 25,542, 1993; *Chem. Abstr.* **1994**, *120*, 245128x.

(3) Oyama, H.; Ono, T.; Tsujimoto, K.; Wada, T. *JP* 61 106,562; *Chem. Abstr.* **1986**, *105*, 226603x.

(4) Levi, S.; Benedi, F.; Bertolini, G.; Gromo, G.; Mizrahi, J.; Sala, A. *WO* 04,048, 1995; *Chem. Abstr.* **1995**, *123*, 9449u.

(5) (a) Cecchetti, V.; Cruciani, G.; Filipponi, E.; Fravolini, A.; Tabarrini, O.; Xin, T. *Bioorg. Med. Chem.* **1997**, *5*, 1339. (b) CIBA Ltd. *Fr.* 1,555,544, 1969; *Chem. Abstr.* **1970**, *72*, 55468a.

(6) Lopatina, K. I.; Artemenko, G. N.; Sokolova, T. V.; Salimov, R. V.; Vikhlayaev, Yu. I.; Zagorevskii, V. A. *Khim.-Farm. Zh.* **1978**, *12*, 65; *Chem. Abstr.* **1978**, *89*, 109315v.

(7) Palaska, E.; Erdogan, H.; Sakak, C.; Sarac, S.; Yulug, N.; *Turk. J. Med. Sci.* **1993**, *18*, 209; *Chem. Abstr.* **1994**, *120*, 129372y.

(8) (a) Hari, A.; Miller, B. L. *Organic Lett.* **2000**, *2*, 3667. (b) Fernandes, M. A.; Reid, D. H. *Synlett* **2003**, 2231.

(9) (a) Senthilvelan, A.; Ramakrishnan V. T. *Tetrahedron* **2002**, *43*, 5119. (b) Senthilvelan, A.; Thirumalai, D.; Ramakrishnan, V. T. *Tetrahedron* **2004**, *60*, 851.

(10) Benedini, F.; Bertolini, G.; Ferrario, F.; Guindani, R.; Sala, A. *J. Heterocycl. Chem.* **1994**, *31*, 1589.

(11) Kajino, M.; Kawada, A.; Nakayama, Y.; Kimura, H. *WO* 2003020719; *Chem. Abstr.* **2003**, *138*, 238199.

(12) Szabó, J.; Bani-Akoto, E.; Szent-Györgi, A.; Fodor, L.; Sohár, P. *J. Heterocycl. Chem.* **1992**, *29*, 1513.

(13) Fodor, L.; Bernáth, G.; Sinkkonen J.; Pihlaja, K. *J. Heterocycl. Chem.* **2002**, *39*, 927.

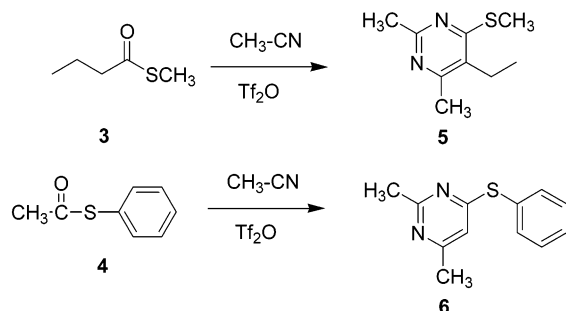
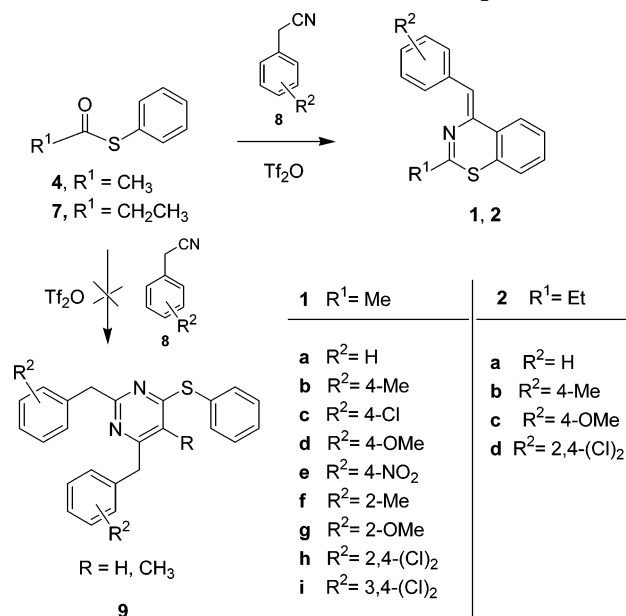
(14) Schmidt, M.; Meier H.; Saleh, S. A. *J. Heterocycl. Chem.* **1991**, *28*, 573.

(15) Hucher N.; Daich, A.; Netchitaïlo, P. *Tetrahedron Lett.* **1999**, *40*, 3363.

(16) Katritzky, A. R.; Xu, Y.-J.; Jain, R. *J. Org. Chem.* **2002**, *67*, 8234.

(17) Zhu, X.; Yu, Qian-sheng.; Greig, N. H.; Flippen-Anderson, J. L.; Brossi, A. *Heterocycles* **2003**, *59*, 115.

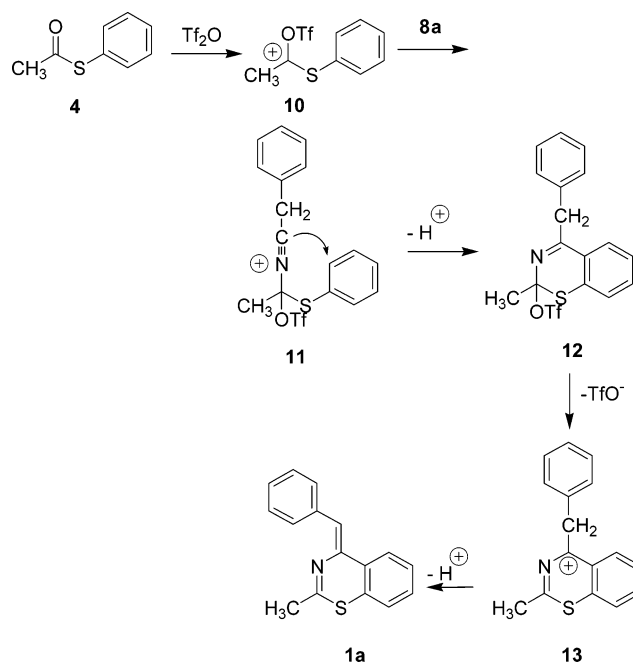
(18) García Martínez, A.; Herrera Fernández, A.; Moreno Jiménez, F.; García Fraile, A.; Subramanian, L. R.; Hanack, M. *J. Org. Chem.* **1992**, *57*, 1627.

**SCHEME 1. Reaction of *S*-Alkyl and *S*-Aryl Thioesters with Acetonitrile and Triflic Anhydride****SCHEME 2. Reaction of *S*-Phenyl Thioesters 4, 7 with Substituted Benzyl Nitriles 8 and the Benzothiazines 1 and 2 That Were Prepared**

$\alpha$ -haloketones and aliphatic esters leads to 5-halopyrimidines<sup>19</sup> and 4-alkoxypyrimidines,<sup>20</sup> respectively. Recently, we reported a new synthetic procedure for the preparation of 4-alkylthio- (5) and 4-arylthiopyrimidines (6) based on the reaction of *S*-alkyl and *S*-arylthioesters (3 and 4) with alkyl or aryl nitriles and triflic anhydride<sup>21</sup> (Scheme 1).

In the present work, we wish to report that the reaction of *S*-phenyl ethanethioate (4) and *S*-phenyl propanethioate (7) with substituted benzyl nitriles (8) in the presence of triflic anhydride produces substituted (4*Z*)-2-alkyl-4-benzylidene-4*H*-1,3-benzothiazines (1, 2) in moderate yields (35–60%). Surprisingly, the formation of 2,6-dibenzyl-4-phenylthiopyrimidines (9) was not observed (Scheme 2).

**Synthesis of Substituted 2-Alkyl-4-benzylidene-4*H*-1,3-benzothiazines.** *S*-Phenyl ethanethioate (4) is known to react with 2 equiv of alkyl or aryl nitriles in

**SCHEME 3. Postulated Mechanism for the Formation of the (4*Z*)-Benzylidene-2-methyl-4*H*-1,3-benzothiazine 1a**

the presence of triflic anhydride to form 4-alkylthio- or 4-arylthiopyrimidines 5 and 6, respectively.<sup>21</sup> However, when the reaction was carried out with benzyl nitriles (8) only substituted 4-benzylidene-2-methyl-4*H*-1,3-benzothiazines (1) were isolated and benzyl pyrimidines (9) were not observed. Moreover, *Z* isomers of compounds 1 were exclusively obtained. The change of the reaction pathway to form 1 can be explained by the nature of possible intermediates involved in the mechanism proposed for this reaction<sup>18</sup> (Scheme 3).

In the proposed mechanism, *S*-phenyl ethanethioate 4 reacts with triflic anhydride forming the triflyloxycarbenium ion 10 which undergoes a nucleophilic attack by a nitrile molecule leading the immonium stabilized nitrilium ion 11.<sup>18</sup> A ring closure through an intramolecular aromatic substitution takes place on the activated ortho position of the *S*-phenyl ring of 11 affording the intermediate 12.

The easy elimination of the triflate group from 12 affords the allylic-type cation 13 (Scheme 3). Proton elimination from 13 leads to stereoselective formation of 1a in synthetically useful yields. A side reaction leading to tris(thiophenyl) orthoacetate CH<sub>3</sub>C(SC<sub>6</sub>H<sub>5</sub>)<sub>3</sub> (14) and (phenyldithio)benzene C<sub>6</sub>H<sub>5</sub>SSC<sub>6</sub>H<sub>5</sub> (15) was observed<sup>21,22</sup> (Supporting Information).

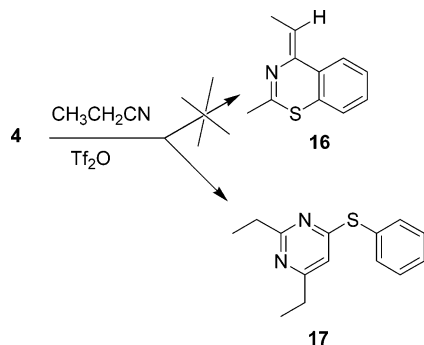
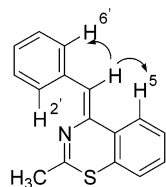
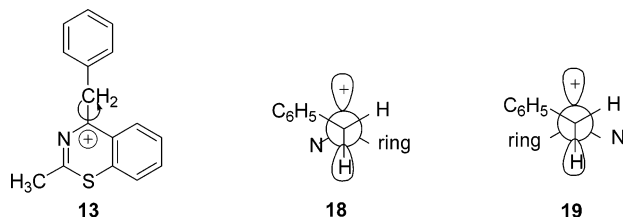
To test other nitriles bearing a methylene group bonded to a cyano function we investigated the reaction of *S*-phenyl ethanethioate 4 with propanenitrile (Scheme 4). In the <sup>1</sup>H NMR spectra of the crude reaction mixture, a sharp singlet at around 6.4 ppm ruled out formation of benzothiazine structure 16, which has been expected to display a quartet at this approximate chemical shift. After the corresponding workup, only pyrimidine 17 was isolated. This fact clearly indicates that the formation of

(19) García Martínez, A.; Herrera Fernández, A.; Molero Vilchez, D.; Subramanian, L. R.; Hanack, M. *Synthesis* **1992**, 1053.

(20) García Martínez, A.; Herrera Fernández, A.; Martínez-Alvarez, R.; Molero Vilchez, D.; Subramanian, L. R. *Tetrahedron* **1999**, 55, 4825.

(21) Herrera, A.; Martínez-Alvarez, R.; Ramiro, P. *Tetrahedron* **2003**, 59, 7331.

(22) Billard, T.; Langlois, B. R.; Large, S.; Anker, D.; Roidor, N.; Roure, P. *J. Org. Chem.* **1996**, 61, 7545.

**SCHEME 4.** Reaction of *S*-Phenyl Ethanethioate 4 with Propanenitrile and Tf<sub>2</sub>O**SCHEME 5.** NOESY Experiments with the Model Compound 1a**SCHEME 6.** Conformers for the Proton Elimination from 13

benzothiazines is made possible by the benzyl group of the nitrile.

The corresponding *E* isomers of **1** and **2** were not detected in any of the examples studied. The complete assignment of the structure of **1** and **2** was achieved from 2D HMBC and HMQC spectra. NOESY spectra revealed cross-peaks between the olefinic proton which appears as a singlet at around 6.45 ppm and the aromatic proton attached to C-5 (Scheme 5). Moreover, there are cross-peaks observed between the olefinic proton and the ortho (H-2' and H-6') positions of the phenyl ring of the benzylidene group. The total assignment of the protons of the phenyl rings was carried out by selective irradiations. Structure elucidation of **1i** was confirmed by an X-ray crystallographic determination (Supporting Information).

Differences in the stabilities of isomeric *Z*- and *E*-benzothiazines **1**, **2** (Scheme S8 and Table S1, Supporting Information) are not significant enough to explain the observed stereoselectivity. Thus, the observed stereoselectivity seems to be controlled by the steric requirements for the proton elimination from **13** (Scheme 3). According to this hypothesis, we have calculated the relative stabilities of the conformers of **13** around the C4–CH<sub>2</sub>C<sub>6</sub>H<sub>5</sub> bond using molecular mechanics (AM1 and PM3) as implemented in Hyperchem 7.0 program. Thus, conformers with an *anti* disposition of the empty *p*-orbital

**TABLE 1.** Heats of Formation ( $\Delta H_f$  in kJ mol<sup>-1</sup>) of Conformers **18** and **19**

conformer	$\Delta H_f$ (AM1)	$\Delta H_f$ (PM3)
<b>18</b>	-1240.45	-1239.53
<b>19</b>	-1490.17	-1448.45

and the hydrogen to be eliminated which present the phenyl ring and the nitrogen atom in gauche disposition **18** are much more stable than **19** (Scheme 6 and Table 1). Energy difference values between conformers are in agreement with the observed stereoselectivity of the process.

In summary, a novel approach to substituted 2-alkyl-(4*Z*)-benzylidene-4*H*-1,3-benzothiazines was successfully achieved by direct one-pot reaction of aryl thioesters with substituted benzyl nitriles and triflic anhydride. The reaction is stereoselective, forming only the corresponding *Z* isomer. The methodology was applied for a wide range of substituted benzyl nitriles.

### Experimental section

Triflic anhydride was prepared from TfOH and distilled twice over P<sub>2</sub>O<sub>5</sub> before use.

**Synthesis of Substituted 2-Alkyl-(4*Z*)-4-benzylidene-4*H*-1,3-benzothiazine **1**, **2**.** To a solution of *S*-phenyl ethanethioate **4** or *S*-phenyl propanethioate **7** (6.5 mmol) and the corresponding substituted phenylacetonitrile **8** (33.6 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> was added triflic anhydride (3.55 g, 12.6 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) dropwise at -78 °C. The mixture was stirred for 1 h at this temperature and allowed to stand at 0 °C during 3 days. The progress of the reaction was monitored by TLC. The reaction mixture was hydrolyzed by careful addition of saturated NaHCO<sub>3</sub>. The organic layer was separated, washed with brine, and dried over MgSO<sub>4</sub>. The solvent was evaporated in vacuo, and the residue was purified by column chromatography (eluent EtOAc/hexanes = 1/99).

**(4*Z*)-4-(3,4-Dichlorobenzylidene)-2-methyl-4*H*-1,3-benzothiazine (**1i**):** yellow needles (from EtOH); yield 41%; mp 90–91 °C; <sup>1</sup>H NMR  $\delta$  2.52 (s, 3H, CH<sub>3</sub>), 6.30 (s, 1H, =CH), 7.16 (dd, *J* = 7.8, 1.2 Hz, 1H, H-8), 7.31 (td, *J* = 7.8, 1.2 Hz, 1H, H-6), 7.37 (td, *J* = 7.8, 1.2 Hz, 1H, H-7), 7.40 (d, *J* = 8.4 Hz, 1H, H-5'), 7.67 (dd, *J* = 7.8, 1.2 Hz, 1H, H-5), 7.69 (dd, *J* = 8.4, 1.9 Hz, 1H, H-6'), 8.13 (d, *J* = 1.9 Hz, 1H, H-2'); <sup>13</sup>C NMR  $\delta$  27.6 (CH<sub>3</sub>), 116.1 (=CH), 125.3 (C-5), 125.7 (C-8), 126.0 (C-8a), 128.4 (C-6), 128.4 (C-7), 129.3 (C-6'), 129.4 (C-4a), 129.8 (C-5'), 130.1 (C-1'), 131.6 (C-2'), 132.0 (C-3'), 136.8 (C-4'), 141.0 (C-4), 157.4 (C-2); MS (EI) *m/z* (%B) 319 (M<sup>+</sup>, 100), 304 (M – CH<sub>3</sub>, 29), 278 (M – CH<sub>3</sub>CN, 65), 208 (278 – 2Cl, 43); IR (KBr)  $\nu$  1603, 1474, 1150, 766 cm<sup>-1</sup>. Anal. Calcd for C<sub>16</sub>H<sub>11</sub>Cl<sub>2</sub>NS: C, 60.01; H, 3.46; Cl, 22.14; N, 4.37; S, 10.01. Found: C, 59.79; H, 3.15; Cl, 21.69; N, 3.89; S, 9.88.

**Acknowledgment.** We thank the DGESIC (Spain, Grant No. BQU2002-00406) for financial support and the CAIs of the UCM (Madrid, Spain) for determining spectra and CHN analyses. We thank also Dr. J. Almy (CSU, Stanislaus, CA) for helpful discussions.

**Supporting Information Available:** Schemes S1–S8, Experimental Section, characterization data for compounds **1**, **2**, **14**, **15**, and **17**, crystallographic data for compound **1i**, <sup>1</sup>H and <sup>13</sup>C NMR spectra for compounds **1a–m**, **14**, **15**, and **17**, and 2D NMR spectra for compound **1i**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

JO049777R