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Regioselective cyclization of chloroacylaminobenzenesulfonamide derivatives

Marina M. Carrozzo [a], Umberto M. Battisti [b], Giuseppe Cannazza [b,*], Cinzia Citti [a], Carlo Parenti [b], Luigino Troisi [a,*]

[a] Dipartimento di Scienze e Tecnologie Biologiche ed Ambientali, Università del Salento, via Prov.le Lecce-Monteroni, 73100 Lecce, Italy
[b] Dipartimento di Scienze Farmaceutiche, Università degli Studi di Modena e Reggio Emilia, Via Campi 183, 41125 Modena, Italy

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ABSTRACT

Chloroacylaminobenzensulfonamides regioselectively thermally cyclize under solvent free conditions to 1,2,4-benzothiadiazines with five- and six-membered rings fused on face b.

Benzothiadiazines represent an important scaffold in pharmaceutical field due to their biological properties such as diuretics, antitumor, and antiviral agents, ATP-sensitive potassium channel activators and positive allosteric modulators of AMPA receptors (AMPApams).[1–4]

In particular, benzothiadiazines with a pyrrolo ring fused on face c as (±)-2,3,3a,4-tetrahydro-1*H*-pyrrolo[2,1-*c*][1,2,4]-benzothiadiazine 5,5-dioxide (**1**) (Fig. 1) have attracted particular attention since in vivo animal experiments demonstrated their cognition enhancing properties, suggesting a potential applicability of this drug as a nootropic agent.[5–14] Moreover 1,2,4-benzothiadiazines with the ring fused on face b are important scaffold of biological interests such as antitumor and antiviral agents.[15,16]

Since only few publications reported the synthesis of this important class of heterocycles,[15–21] it becomes important to develop a simple and versatile synthetic pathway to obtain 1,2,4-benzothiadiazine 1,1-dioxide with a ring condensed on face b and/or on face c.

A common strategy for the synthesis of 1,2,4-benzothiadiazines with the ring fused on face c involves the annulations of chloroacylaminobenzenesulfonamides (**3**,**4**) as reported in Scheme 1.[17–21] It was possible to obtain 2,3-dihydro-1*H*-pyrrolo[2,1-*c*][1,2,4]benzothiadiazine 5,5-dioxide (**6**) and 3-chloro-7,8,9,10-tetrahydropyrido[2,1-*c*][1,2,4]benzothiadiazine 5,5-dioxide (**7**) in excellent yields (98%) by refluxing 2-(γ-chlorobutyryl)-5-chloroaminobenzenesulfonamide (**3**) and 2-(δ-chlorovaleryl)-5-chloroaminobenzenesulfonamide (**4**) in NaOH at 2% for 15 min, respectively. 2-(6-Chlorohexanoyl)-5-chloroaminobenzenesulfonamide (**5**) refluxed in NaOH gave quantitatively the corresponding 7-chloro-3-(5-chloropenthyl)-2*H*-1,2,4-benzothiadiazine 1,1-dioxide (**10**) and not the expected 3-chloro-8,9,10,11-tetrahydro-7*H*-azepino[2,1-*c*][1,2,4]benzothiadiazine 5,5-dioxide (**11**) (Scheme 2).

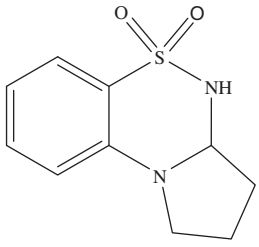

Figure 1. (±)-2,3,3a,4-Tetrahydro-1*H*-pyrrolo[2,1-*c*][1,2,4]-benzothiadiazine 5,5-dioxide (**1**).

The subsequent reduction with lithium aluminium hydride furnished the corresponding 1,2,4-dihydrobenzothiadiazine derivatives with five- and six-membered rings fused on face c (**8**,**9**).

Due to the biological importance of benzothiadiazine with the ring fused on face b, we have tentatively varied the reaction conditions in order to cyclize chloroacylaminobenzensolfonamides regioselectively on face b. Since 1,2,4-benzothiadiazines with the ring fused on face c were obtained in basic media, in a first attempt the cyclization reaction was performed in neutral and acidic media. Anyway only starting material was isolated when the pH was

* Corresponding authors. Tel.: +39 059 2055136; fax: +39 059 2055750.
E-mail addresses: giuseppe.cannazza@unimore.it (G. Cannazza), luigino.troisi@unisalento.it (L. Troisi).

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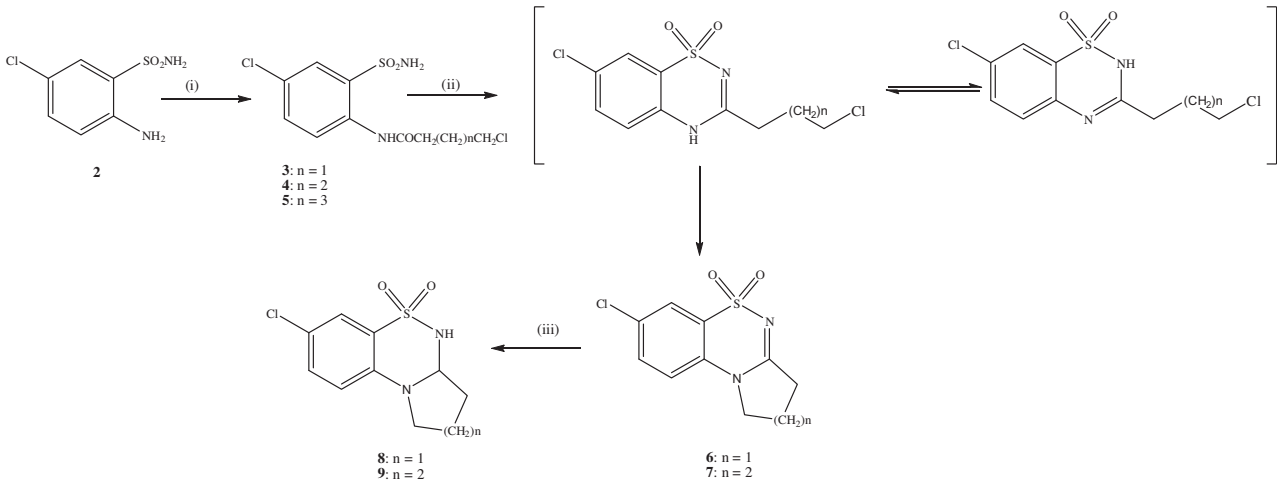
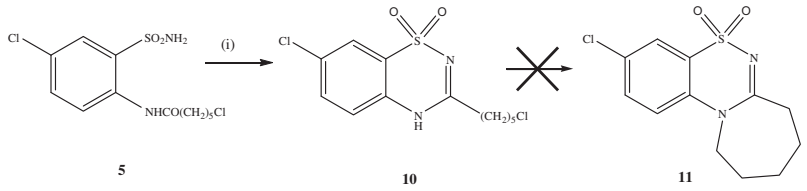


Scheme 1. Reagents and conditions: (i) chloroacyl chloride (2 equiv), *N*,*N*-DMA, 0 °C; (ii) NaOH (2%) (3 equiv), 100 °C, 15 min; (iii) $LiAlH_4$ (2 equiv), diethylether, −10 °C.



Scheme 2. Reagent and conditions: (i) NaOH refluxed; 250 °C 15 min.

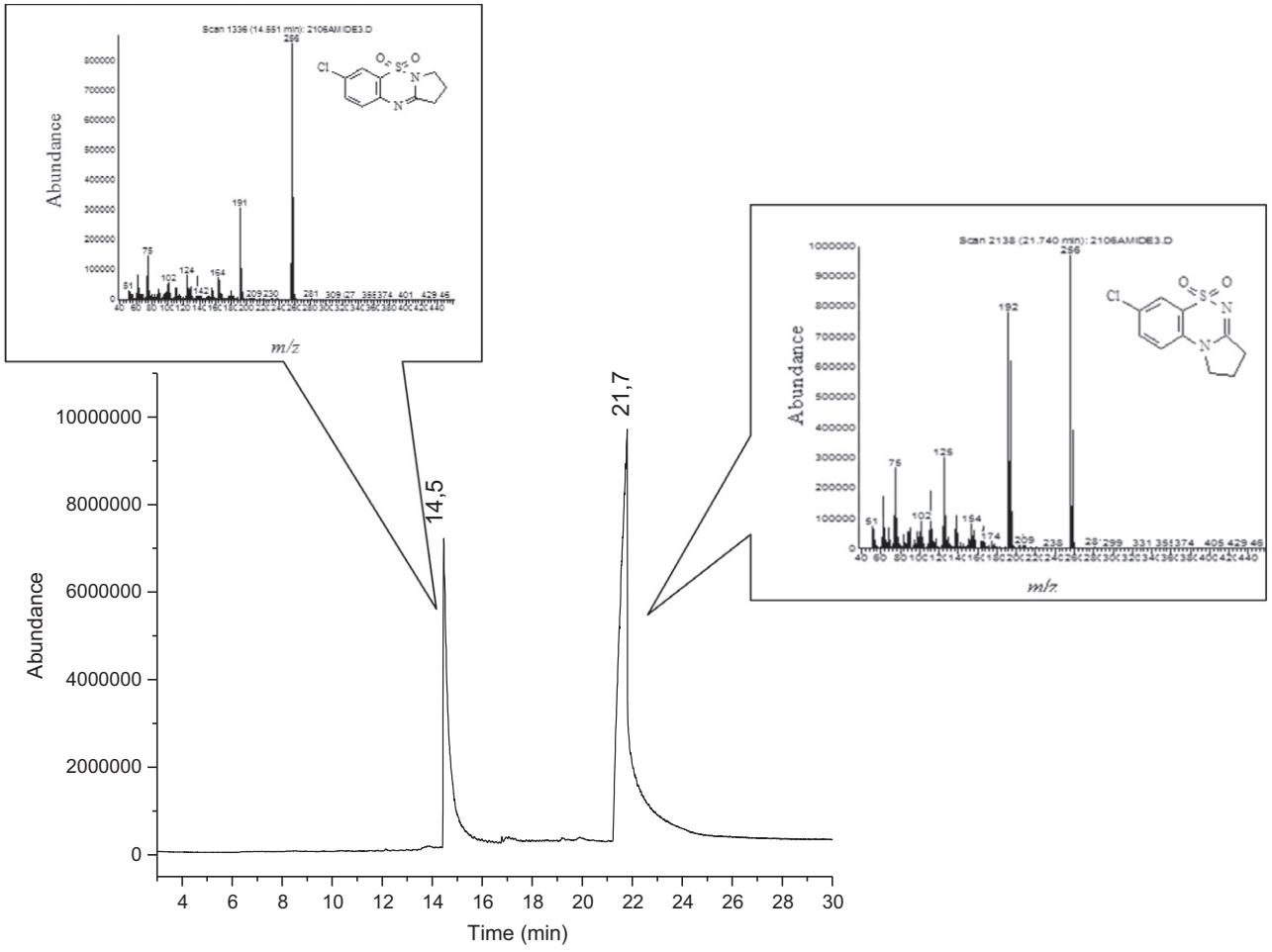
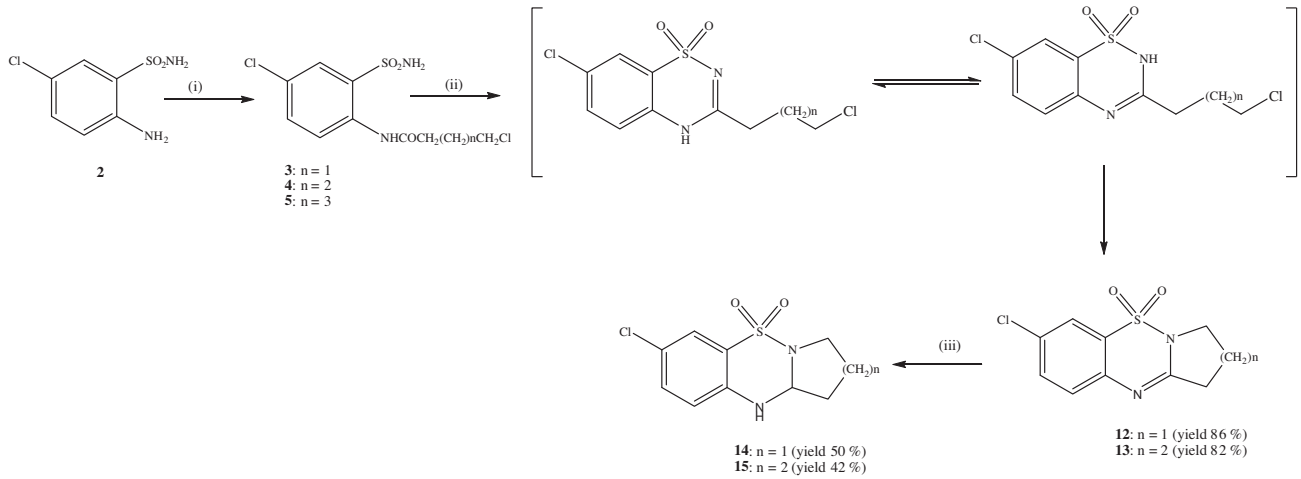


Figure 2. GC–MS chromatogram of **3**.



Scheme 3. Reagents and conditions: (i) chloroacylchloride (2 equiv), *N*,*N*-DMA, 0 °C; (ii) 250 °C, 15 min; (iii) $LiAlH_4$ (2 equiv), diethylether, −10 °C.

lower than 7. Moreover no cyclization occurred when the reaction was performed in different solvents such as 2-propanol, acetonitrile, and ethyl acetate at their refluxed temperatures.

An important indication to prepare 1,2,4-benzothiadiazine with the ring fused on face b was obtained by injection of chloroacylaminobenzensulfonamides (**3**,**4**) in GC–MS. Injection of **3** furnished a chromatogram with two peaks with the same molecular ion corresponding to the cyclized 1,2,4-benzothiadiazine **6** (Fig. 2). As a consequence authentic **6** was injected into GC–MS and the retention time and fragmentation spectrum were superimposable to those of second eluted peak obtained by injection of **3**. This result indicated that the second eluted peak corresponded to the cyclization product of **3** with the ring fused on face c (**6**).

We hypothesized that the first eluted peak (with the same molecular ion of the second peak eluted corresponding to **6**) was the isomer of **6** with the ring fused on face b (Fig. 2). In order to confirm the identity of the first eluted peak, 7-chloro-2,3-dihydro-1*H*-pyrrolo[1,2-*b*][1,2,4]benzothiadiazine 5,5-dioxide (**12**) was prepared as reported in the literature and injected into GC–MS.[16]Authentic **12** eluted with the same retention time with a fragmentation spectrum superimposable to that of the first eluted peak obtained by injection of **3**.

The results obtained indicated that **3**, when injected into GC–MS, cyclized to give two isomers of 1,2,4-benzothiadiazine with a ring fused on face b and on face c (Fig. 2).

The cyclization process of **3** observed in GC–MS, can occur in the injector (270 °C for about 0.7 min) or during the chromatographic run. In the literature it is reported that when a compound reacts during a chromatographic run, a characteristic plateau appears in the chromatogram due to an on column reaction of the compound injected.[22] The absence of characteristic plateau in the chromatograms obtained by injection in GC–MS of **3** suggested that it cyclized in the injector rather than in the column.

In the efforts to reproduce the same conditions that chloroacylaminobenzenesulfonamides met in the injector, compounds **3** and **4** were heated under solvent free conditions at temperature over their melting points (about 250 °C) for at least 10 min. Surprisingly, under these reaction conditions the corresponding 1,2,4-benzothiadiazines derivatives with the ring fused on face b were obtained in high yields (Scheme 3). Probably the absence of solvation by the solvent and the high temperature promote 2*H*-tautomer of 1,2,4-benzothiadiazine forcing the cyclization of chloroacylaminobenzenesulfonamides regioselectively toward annulations on face b. Anyway thermal cyclization of 2-(6-chlorohexanoyl)-5-chloroaminobenzenesulfonamide (**5**) did not lead to the corresponding 3-chloro-8,9,10,11-tetrahydro-7*H*-azepino[2,1-*c*][1,2,4]benzothiadiazine 5,5-dioxide but to 7-chloro-3-(5-chloropenthyl)-2*H*-1,2,4-benzothiadiazine 1,1-dioxide (**10**) without further cyclization (Scheme 2). The same result was obtained when the cyclization of **5** was performed in refluxed NaOH (Scheme 2).

The last step was the saturation of the double bond of thiadiazide ring (Scheme 3).[17–21] This was achieved by the action of lithium aluminium hydride leading to final dihydrobenzothiadiazines with the five- and six-membered ring fused on face b (**14** and **15**)

In conclusion, the results obtained have suggested a simple and versatile synthetic strategy for the preparation of two different pharmacological relevant scaffolds. Starting from chloroacylbenzenesulfonamides, it was possible to obtain selectively 1,2,4-benzothiadiazines with five- and six-membered rings fused on face c and on face b in one pot.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.04.009.

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