Tetrahedron Letters 51 (2010) 4433–4436

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

# Regioselective reduction of 3-substituted 2,3-dihydrobenzothiadiazines with borohydrides

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ARTICLE INFO

*Article history:*
Received 12 May 2010
Revised 14 June 2010
Accepted 16 June 2010
Available online 20 June 2010

*Keywords:*
2-Aminobenzenesulfonamide
3-Chiral 2,3-dihydrobenzothiadiazines
Reduction
Sodium cyanoborohydride

ABSTRACT

A simple and efficient synthetic path for N-1 or N-2 alkyl-substituted 2-aminobenzenesulfonamides was developed based on regioselective reduction with $NaBH_3CN$ in different solvents.



The chemistry of 2-aminobenzenesulfonamide is extensively studied because it represents an important scaffold in pharmaceutical chemistry.[1–5] Recently 5-chloro-2-(methylamino)benzene sulfonamide and 5-chloro-2-(ethylamino)benzenesulfonamide have been proposed as positive allosteric modulators of AMPA receptor suggesting a possible use as nootropic drugs.[6] In this work a possible synthetic route is proposed to obtain different substituted 2-aminobenzenesulfonamides at the sulfonamidic or anilinic nitrogen atom. Recently, we demonstrated that some derivatives of chiral C-3 2,3-dihydrobenzothiadiazines undergo a rapid racemization in protic solvents.[7–9] It was hypothesized that the racemization involves the formation of an imine intermediate with the double bond at N-2 C-3 or C-3 N-4 depending on the nature of the substituents and on the pH of the racemization solvent (Scheme 1).[10] Starting from the proposed mechanism, the selected chiral 2,3-dihydrobenzothiadiazine, (±)-7-chloro-3-methyl-3,4-dihydro-2*H*-1,2,4-benzothiadiazine 1,1-dioxide (IDRA21, **1**), was subjected to the action of imine-reducing agents. As previously reported by Biressi et al. we tested on **1** the action of sodium borohydride ($NaBH_4$) in methanol and of triethylamino borane in acetic acid obtaining, respectively, 2-amino-5-chloro-*N*-ethylbenzenesulfonamide (**1b**) and 5-chloro-2-(ethylamino)benzenesulfonamide (**1a**).[11] In the attempt to explain if the results of the reduction depend on reductive agents or solvent conditions, sodium cyanoborohydride ($NaBH_3CN$) was selected because it is presently the most successful and often used reductive agent for imine reductions and it is effective with different solvent conditions. When compound **1** was treated with $NaBH_3CN$ in glacial acetic acid at room temperature, **1a** was obtained in 93% yield (Table 1, entry 1).[12] Differently, when compound **1** was treated with $NaBH_3CN$ under water/alcoholic conditions **1b** was isolated in 86% yield (Table 1, entry 2).[13] The results could be explained with the formation of two different imine intermediates depending on the pH of the reaction mixture. Using glacial acetic acid as the solvent the protonation of N-2 led to the C-3 N-4 imine intermediate that was subsequently reduced by $NaBH_3CN$ giving **1a** (Scheme 2). Using water/ethanol (1:3 (v/v)) as the solvent, the dissociation of the more acidic sulfonamidic nitrogen promoted by the electron-withdrawing effect of the sulfone moiety led to N-2 C-3 imine intermediate giving **1b** in good yields (89%) by the action of $NaBH_3CN$ (Scheme 2). Interestingly in the latter conditions 2-amino-5-chlorobenzenesulfonamide was isolated in 10% yield. Its formation could be explained by the hydrolysis of the imine intermediate as reported in Scheme 1. In our opinion the rate of the reductive reaction is lowered because $NaBH_3CN$ is a less effective reducing agent under neutral/basic than under acidic conditions allowing hydrolysis process. Subsequently different substituted 2,3-dihydrobenzothiadiazines were subjected to the reductive action of $NaBH_3CN$. The results are reported in Table 1. Reduction of compound **2** under acidic conditions led to **2a** (Table 1, entry 3) while in water/ethanol solvent only 2-amino-5-chloro-*N*-ethylbenzenesulfonamide (**1b**) was obtained (Table 1, entry 4). Previously it was reported that no racemization occurred under neutral conditions for 2-alkyl-substituted

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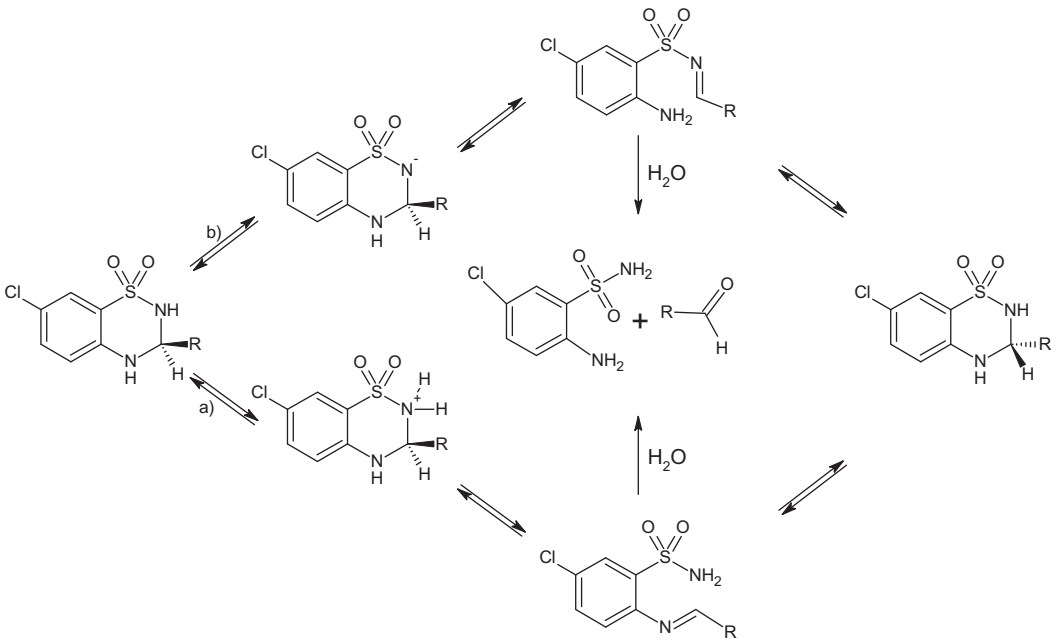
doi:10.1016/j.tetlet.2010.06.081



**Scheme 1.** Possible racemization and hydrolysis mechanism for C-3 chiral 2,3-dihydrobenzothiadiazines. (a) Acid conditions (b) neutral/basic conditions.

**Table 1**
Reduction of 2,3-dihydrobenzothiadiazines with $NaBH_3CN$

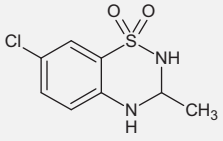
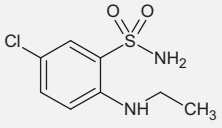
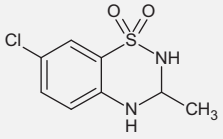
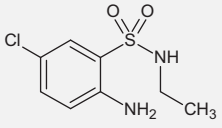
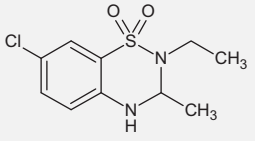
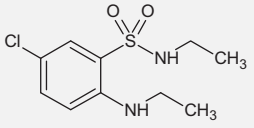
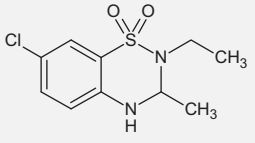
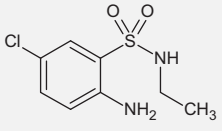
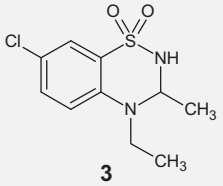
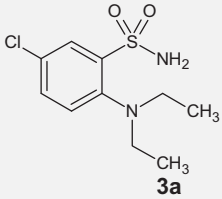
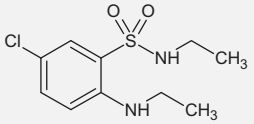
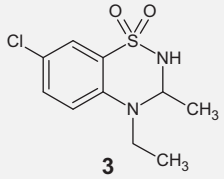
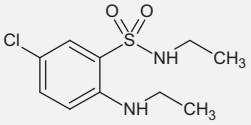
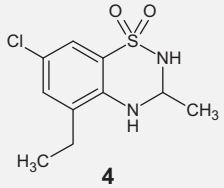
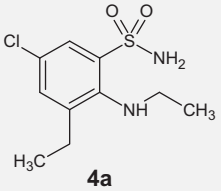
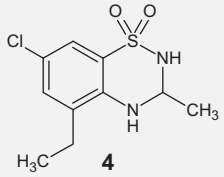
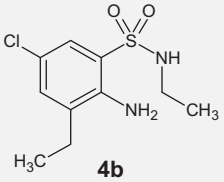
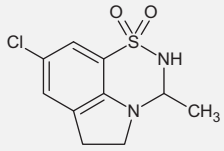
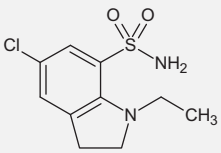
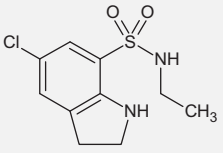
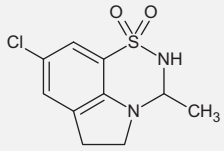
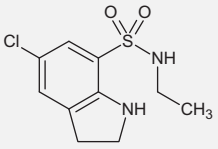
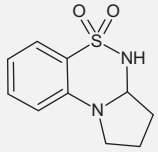
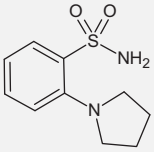
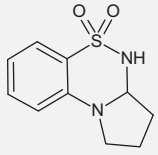
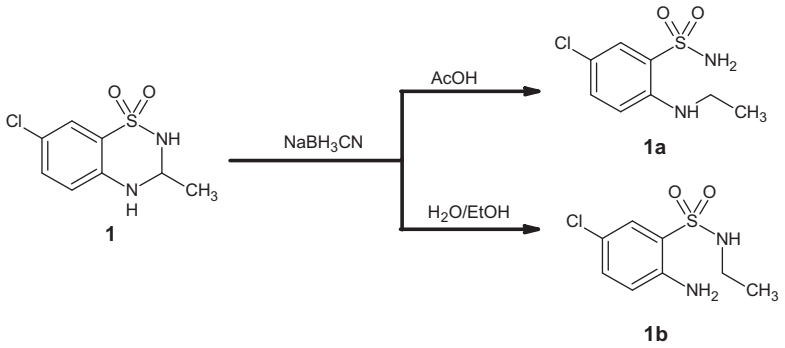
| Entry | Compound | Conditions | Product | Yield[a] (%) |
|---|---|---|---|---|
| 1 |  **1** | a |  **1a** | 93 |
| 2 |  **1** | b |  **1b** | 86 |
| 3 |  **2** | a |  **2a** | 96 |
| 4 |  **2** | b |  **1b** | 95 |
| 5 |  **3** | a |  **3a**  **2a** | —[*] |

**Table 1** (*continued*)

| Entry | Compound | Conditions | Product | Yield[a] (%) |
|---|---|---|---|---|
| 6 |  **3** | b |  **2a** | 89 |
| 7 |  **4** | a |  **4a** | 65 |
| 8 |  **4** | b |  **4b** | 90 |
| 9 |  **5** | a |  **5a**  **5b** | —** |
| 10 |  **5** | b |  **5b** | 91 |
| 11 |  **6** | a |  **6a** | 98 |
| 12 |  **6** | b | — | — |

Reaction conditions a: $NaBH_3CN$ (6.0 equiv) in glacial AcOH at room temperature for 3 h.
Reaction conditions b: $NaBH_3CN$ (6.0 equiv) in water/ethanol 1:3 (v/v) at 70 °C for 6 h.
[a] Isolated yield.
* Isolated in a molar ratio of 1:3, respectively.
** Isolated in a molar ratio of 4:1, respectively.

benzothiadiazines while a rapid racemization under acidic conditions was observed.[8] Probably in water/ethanol the absence of the acid hydrogen on N-2 of **2** prevents the formation of the N-2 C-3 imine intermediate, leading to a rapid thermally induced hydrolysis. Compound **3** in glacial acetic acid reacts with $NaBH_3CN$ giving **2a** and **3a** in a ratio of 3:1, respectively (Table 1, entry 5). The alkyl substituent on N-4 could favor the N-2 C-3 imine intermediate over the C-3 N-4 iminium intermediate. Interestingly when the reduction was performed at lower temperature (10 °C), a mixture of **2a** and **3a** in a 1:1 ratio was obtained suggesting that the C-3 N-4 iminium intermediate is kinetically favored while the N-2 C-3 imine intermediate is thermodynamically more stable. Reduction of **3** in water/ethanol shows, as expected, a complete regioselectivity giving **2a** (Table 1, entry 6). Similar to IDRA21 compound **4** provides a good regioselective reduction giving **4a** (Table 1, entry 7) under acidic conditions and **4b** in water/ethanol (Table 1, entry 8). How-




**Scheme 2.** Reduction of compound **1** with $NaBH_3CN$ in AcOH and in water/ethanol.

ever, it was observed that under acidic conditions the yield of reduction was lower than the one obtained for IDRA21 (65% yield). A longer reaction time (12 h) was required to obtain a 95% yield suggesting that the inductive effect of the ethyl substituent in 5 position could affect reduction timescale. These data are in accordance with the previously observed decreased racemization rate at low pH for chiral 5-alkyl-substituted 2,3-dihydrobenzothiadiazines. Reduction with $NaBH_3CN$ of compound **5** has shown a behavior similar to that observed for **3**: in water/ethanol only **5b** was isolated (Table 1, entry 10), while under acidic conditions **5a** and **5b** were obtained (Table 1, entry 9). Compound **6** was reduced by $NaBH_3CN$ only under acidic conditions to give **6a** (Table 1, entry 11) while in water/ethanol only unchanged starting material was obtained. Previously no racemization was observed for compound **6** under neutral/basic conditions, while it racemizes at low pH indicating that strong acid conditions are required for the iminium intermediate formation.[8] In summary, a new synthetic path for N-1 or N-2 alkyl-substituted 2-aminobenzenesulfonamides was developed based on regioselective reduction with $NaBH_3CN$ in different solvents. This simple method could be adapted for the synthesis of more advanced intermediates.

## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.06.081.

## References and notes

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12. *General procedure a for the reduction of 2,3-dihydrobenzothiadiazines with $NaBH_3CN$*: To a solution of 7-chloro-3-methyl-3,4-dihydro-2*H*-1,2,4 benzothiadiazine-1,1-dioxide (1.0 mmol) in glacial acetic acid (20 ml) $NaBH_3CN$ (6.0 mmol) was added. The resulting mixture was stirred at room temperature for 3 h. The mixture was then neutralized with NaOH 10 M and extracted with ethyl acetate (2 × 20 ml). The organic layer was washed with deionized water and dried over anhydrous sodium sulfate. The solvent was removed under vacuum and the residue was purified by chromatography, eluting with diethyl ether/petroleum ether 1:1, to give the pure product.
13. *General procedure b for the reduction of 2,3-dihydrobenzothiadiazines with $NaBH_3CN$*: $NaBH_3CN$ (6.0 mmol) was added to a solution of 7-chloro-3-methyl-3,4-dihydro-2*H*-1,2,4 benzothiadiazine-1,1-dioxide (1.0 mmol) in 30% aqueous ethanol (20 ml). The mixture was stirred at 70 °C for 6 h. The mixture was neutralized with dil HCl and extracted with ethyl acetate (2 × 20). The organic layer was dried over anhydrous sodium sulfate and the solvent was removed under vacuum. The residue was purified by column chromatography using diethyl ether/petroleum ether 1:1, to give the pure product.