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Denitrocyclisation in the synthesis of dibenzothiazepinones

Alexey V. Smirnov, Levan S. Kalandadze, Vladimir N. Sakharov and Mikhail V. Dorogov*

K. D. Ushinsky Yaroslavl State Pedagogical University, 150000 Yaroslavl, Russian Federation. E-mail: Michael_Dorogov@list.ru

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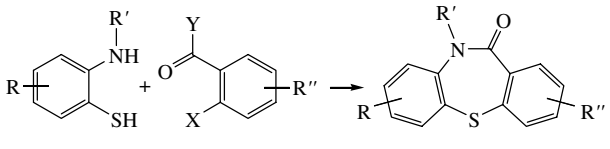
A new method has been elaborated for the synthesis of new compounds of the dibenzothiazepine series by intramolecular aromatic substitution of the nitro group.

Dibenzothiazepines are of interest as potential antivirals, in particular, for AIDS prevention and treatment.[1–3] However, the methods of their synthesis are usually limited to the reaction of *ortho*-aminothiophenols with the derivatives of *ortho*-halobenzoic acids, which does not offer a wide variety of these compounds (Scheme 1).[1–3]

We have developed a new method to synthesise the specified compounds based on the intramolecular aromatic substitution of the nitro group (denitrocyclisation).[4] Unlike the known methods, our method makes it possible to introduce a required substituent at the nitrogen atom even before the ring has formed, using almost any primary amine for this purpose.[1–2]

Thiosalicylic acid **2**, which readily participates in nucleophilic substitution with various activated aromatic substrates, serves as the main reagent in the synthesis. We used 2,4-dinitrochlorobenzene **1** to obtain dibenzothiazepines containing a nitro group, which was then converted into an amino group.



X = F, Cl, Br, I
Y = Cl, OH, OAlk

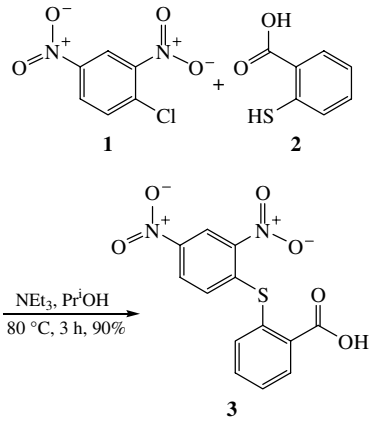
Scheme 1

Intermediate 2-(2,4-dinitrophenylthio)benzoic acid **3** can be obtained in a high yield by heating equimolar amounts of the specified reagents and triethylamine (acceptor of hydrogen chloride) at 80 °C for 3 h (Scheme 2).†

At the next stage of the synthesis of dibenzothiazepines, a solution of 2-(2,4-dinitrophenylthio)benzoyl chloride **4** in dioxane was obtained. Product **4** is used without isolation from solution in the subsequent reaction with primary amines to give corresponding amides **5a–e** (Scheme 3).‡

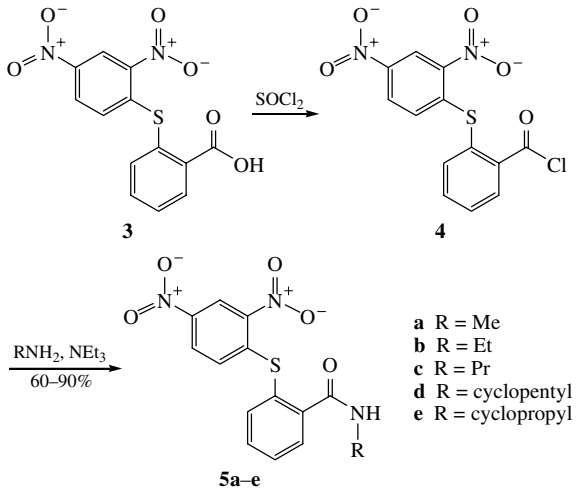
† ^{1}H NMR spectra of 5% solutions in [$^2H_6$]DMSO with TMS as an internal standard were recorded on a Bruker DPX-300 instrument.

2-(2,4-Dinitrophenylthio)benzoic acid **3**. A mixture of 2,4-dinitrochlorobenzene **1** (20.26 g, 0.1 mol), thiosalicylic acid **2** (15.42 g, 0.1 mol), triethylamine (20.24 g, 0.2 mol) and isopropanol (150 ml) was stirred at 80 °C for 3 h; the reaction mixture was then cooled and neutralised with hydrochloric acid. The precipitate that formed was filtered off, washed with water and dried. Yield 90%, mp 220–223 °C. ^{1}H NMR, δ: 8.92 (s, 1H), 8.20 (d, 1H, *J* 8 Hz), 8.00 (d, 1H, *J* 8.1 Hz), 7.65 (m, 3H), 7.06 (d, 1H, *J* 7.9 Hz). Found (%): C, 48.65; H, 2.52; N, 8.70; S, 10.02. Calc. for $C_{13}H_8N_2O_6S$ (%): C, 48.75; H, 2.52; N, 8.73; S, 10.01.

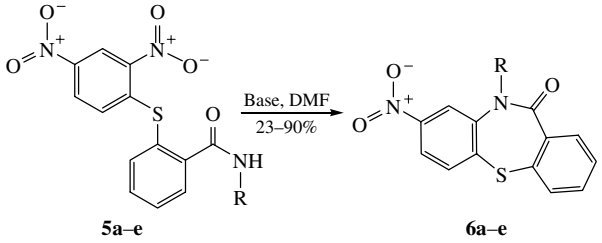


Scheme 2

The formation of a thiazepine ring occurs *via* the nucleophilic replacement of the nitro group with the amide nucleophilic centre that is formed on treatment with deprotonating agents (Scheme 4). If strong bases, such as sodium hydride, sodium amide or potassium *tert*-butylate were used, the reaction occurred even at room temperature. The reaction product was formed in a low yield only if sodium amide was used, perhaps due to a side reaction,



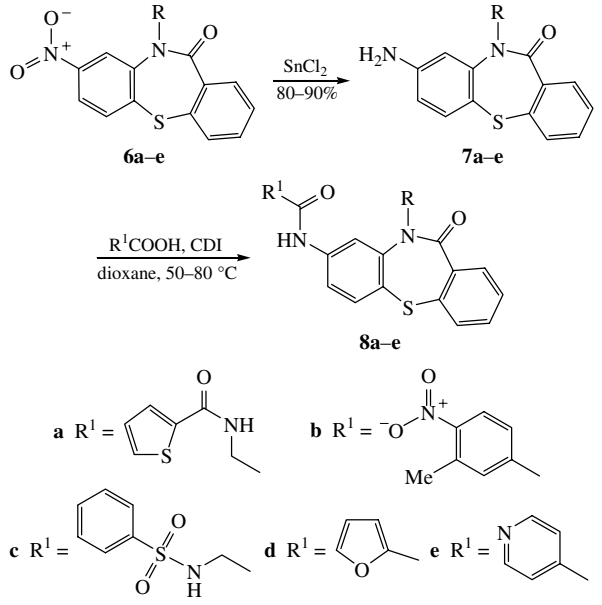
Scheme 3



Scheme 4 *Reagents and conditions*: i, 0–20 °C, 2 h, R = Me, Base = NaH (80%), $NaNH_2$ (23%), KOBu^t (88%); ii, 120 °C, 5 h, R = Me, Base = K_2CO_3 (90%).

e.g., the Chichibabin amination. The use of potassium carbonate as the deprotonating agent also resulted in denitrocyclisation, but only at temperatures no lower than 120 °C. The use of potassium carbonate is beneficial as it becomes unnecessary to use anhydrous DMF, whereas the yields of products **6a–e** remain high (80–90%).§

Another goal of this study was the functionalisation of 8-nitrodibenzothiazepines **6a–e** to corresponding amino **7a–e**¶ and



Scheme 5

‡ Thionyl chloride (13.09 g, 0.11 mol) was added to a suspension of compound **3** (32.03 g, 0.1 mol) in anhydrous dioxane (100 ml). The mixture was stirred for 2 h at 50 °C and cooled, and a solution of a primary amine (0.11 mol) and triethylamine (11.13 g, 0.11 mol) in dioxane (200 ml) was then added dropwise. The reaction mixture was stirred for 2 h, cooled and poured into water. The precipitate that formed was filtered off and dried.

5a: yield 79%, mp 174–176 °C. ^{1}H NMR, δ: 8.95 (s, 1H), 8.20 (m, 2H), 7.60 (m, 4H), 7.00 (d, 1H, *J* 8.1 Hz), 2.70 (s, 3H). Found (%): C, 50.37; H, 3.33; N, 12.65; S, 9.63. Calc. for $C_{14}H_{11}N_3O_5S$ (%): C, 50.45; H, 3.33; N, 12.61; S, 9.62.

5b: yield 82%, mp 143–145 °C. ^{1}H NMR, δ: 8.94 (s, 1H), 8.40 (t, 1H), 8.19 (d, 1H, *J* 8.1 Hz), 7.59 (m, 4H), 6.97 (d, 1H, *J* 8.0 Hz), 3.21 (dd, 2H), 1.02 (t, 3H). Found (%): C, 51.78; H, 3.78; N, 12.09; S, 9.24. Calc. for $C_{15}H_{13}N_3O_5S$ (%): C, 51.87; H, 3.77; N, 12.10; S, 9.23.

5c: yield 86%, mp 93–95 °C. ^{1}H NMR, δ: 8.94 (s, 1H), 8.32 (t, 1H), 8.20 (d, 1H, *J* 8.0 Hz), 7.58 (m, 4H), 7.00 (d, 1H, *J* 8.1 Hz), 3.08 (dd, 2H), 1.40 (m, 2H), 0.80 (t, 3H). Found (%): C, 53.14; H, 4.19; N, 11.60; S, 8.88. Calc. for $C_{16}H_{15}N_3O_5S$ (%): C, 53.18; H, 4.18; N, 11.63; S, 8.87.

5d: yield 90%, mp 140–142 °C. ^{1}H NMR, δ: 8.95 (s, 1H), 8.37 (d, 1H, *J* 8.5 Hz), 8.21 (d, 1H, *J* 8.0 Hz), 7.61 (m, 4H), 7.01 (d, 1H, *J* 8.0 Hz), 4.05 (m, 1H), 1.60 (m, 8H). Found (%): C, 55.79; H, 4.43; N, 10.82; S, 8.29. Calc. for $C_{18}H_{17}N_3O_5S$ (%): C, 55.80; H, 4.42; N, 10.85; S, 8.28.

5e: yield 60%, mp 131–133 °C. ^{1}H NMR, δ: 8.94 (s, 1H), 8.38 (d, 1H, *J* 8.5 Hz), 8.19 (d, 1H, *J* 8.1 Hz), 7.60 (m, 4H), 7.00 (d, 1H, *J* 8.0 Hz), 2.70 (m, 1H), 0.62 (m, 2H), 0.40 (m, 2H). Found (%): C, 53.43; H, 3.65; N, 11.67; S, 8.93. Calc. for $C_{16}H_{13}N_3O_5S$ (%): C, 53.48; H, 3.65; N, 11.69; S, 8.92.

§ Compound **5a–e** (0.1 mol) and potassium carbonate (27.64 g, 0.2 mol) were added to DMF (100 ml). The reaction mixture was stirred for 5 h at 120 °C, cooled and poured into water. The precipitate was filtered off, washed with water and recrystallised from an ethanol–DMF mixture.

6a: yield 90%, mp 187–189 °C. ^{1}H NMR, δ: 8.38 (s, 1H), 8.22 (d, 1H, *J* 8.0 Hz), 7.66 (d, 1H, *J* 8.0 Hz), 7.58 (m, 1H), 7.47 (m, 1H), 7.36 (m, 2H), 3.60 (s, 3H). Found (%): C, 58.66; H, 3.52; N, 9.80; S, 11.22. Calc. for $C_{14}H_{10}N_2O_3S$ (%): C, 58.73; H, 3.52; N, 9.78; S, 11.20.

6b: yield 85%, mp 119–121 °C. ^{1}H NMR, δ: 8.37 (s, 1H), 8.20 (d, 1H, *J* 8.0 Hz), 7.63 (d, 1H, *J* 8.0 Hz), 7.56 (m, 1H), 7.45 (m, 1H), 7.34 (m, 2H), 4.57 (dd, 1H), 3.51 (dd, 1H), 1.21 (t, 3H). Found (%): C, 59.89; H, 4.03; N, 9.37; S, 10.69. Calc. for $C_{15}H_{12}N_2O_3S$ (%): C, 59.99; H, 4.03; N, 9.33; S, 10.67.

6c: yield 80%, mp 117–119 °C. ^{1}H NMR, δ: 8.40 (s, 1H), 8.22 (d, 1H, *J* 8.0 Hz), 7.86 (d, 1H, *J* 8.0 Hz), 7.60 (t, 1H), 7.52 (d, 1H, *J* 8.1 Hz), 7.42 (m, 2H), 4.60 (m, 1H), 3.70 (m, 1H), 1.60 (m, 2H), 0.90 (t, 3H). Found (%): C, 61.05; H, 4.49; N, 8.88; S, 10.21. Calc. for $C_{16}H_{14}N_2O_3S$ (%): C, 61.13; H, 4.49; N, 8.91; S, 10.20.

6d: yield 87%, mp 157–159 °C. ^{1}H NMR, δ: 8.40 (s, 1H), 8.21 (d, 1H, *J* 8.0 Hz), 7.85 (d, 1H, *J* 8.0 Hz), 7.61 (t, 1H), 7.51 (d, 1H, *J* 8.1 Hz), 7.41 (m, 2H), 4.50 (m, 1H), 2.00–1.50 (m, 8H). Found (%): C, 63.46; H, 4.74; N, 8.20; S, 9.43. Calc. for $C_{18}H_{16}N_2O_3S$ (%): C, 63.51; H, 4.74; N, 8.23; S, 9.42.

6e: yield 82%, mp 153–155 °C. ^{1}H NMR, δ: 8.37 (s, 1H), 8.27 (d, 1H, *J* 8.0 Hz), 7.83 (d, 1H, *J* 8.0 Hz), 7.70 (m, 1H), 7.52 (m, 1H), 7.42 (m, 2H), 3.50 (m, 1H), 1.22 (m, 1H), 0.80 (m, 2H), 0.05 (m, 1H). Found (%): C, 61.47; H, 3.88; N, 8.95; S, 10.27. Calc. for $C_{16}H_{12}N_2O_3S$ (%): C, 61.53; H, 3.87; N, 8.97; S, 10.26.

amido derivatives **8a–e**.†† Nitro derivatives were reduced chemically using tin(II) chloride as a reducing agent. The final stage involved acylation using acylimidazoles obtained *in situ* from acids and carbonyldiimidazole as the reagents (Scheme 5).

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¶ Compound **6a–e**, tin dichloride dihydrate (78.96 g, 0.35 mol) and 30% hydrochloric acid (85 ml, 0.7 mol) were added to 100 ml of ethanol. The mixture was stirred for 2 h at 80 °C, cooled and poured into a solution of sodium hydroxide (40 g, 1 mol) in water (300 ml). The precipitate was filtered off, washed with water and reprecipitated from DMF.

7a: yield 93%, mp 227–229 °C. ^{1}H NMR, δ: 7.50 (d, 1H, *J* 8.1 Hz), 7.41 (d, 1H, *J* 8.1 Hz), 7.29 (m, 2H), 7.11 (d, 1H, *J* 8.0 Hz), 6.72 (s, 1H), 6.50 (d, 1H, *J* 8.2 Hz), 5.26 (s, 2H), 3.52 (s, 3H). Found (%): C, 65.50; H, 4.72; N, 10.95; S, 12.52. Calc. for $C_{14}H_{12}N_2OS$ (%): C, 65.60; H, 4.72; N, 10.93; S, 12.51.

7b: yield 84%, mp 181–183 °C. ^{1}H NMR, δ: 7.52 (d, 1H, *J* 8.1 Hz), 7.38 (d, 1H, *J* 8.1 Hz), 7.29 (t, 2H), 7.00 (d, 1H, *J* 8.0 Hz), 6.73 (s, 1H), 6.50 (d, 1H, *J* 8.1 Hz), 4.90 (s, 2H), 4.50 (dd, 1H), 3.45 (dd, 1H), 1.18 (t, 3H). Found (%): C, 66.57; H, 5.22; N, 10.33; S, 11.88. Calc. for $C_{15}H_{14}N_2OS$ (%): C, 66.64; H, 5.22; N, 10.36; S, 11.86.

7c: yield 82%, mp 172–174 °C. ^{1}H NMR, δ: 7.50 (d, 1H, *J* 8.1 Hz), 7.41 (d, 1H, *J* 8.1 Hz), 7.29 (m, 2H), 7.10 (d, 1H, *J* 8.0 Hz), 6.72 (s, 1H), 6.51 (d, 1H, *J* 8.2 Hz), 5.30 (s, 2H), 4.45 (m, 1H), 3.36 (m, 1H), 1.50 (m, 2H), 0.90 (t, 3H). Found (%): C, 67.53; H, 5.68; N, 9.82; S, 11.29. Calc. for $C_{16}H_{16}N_2OS$ (%): C, 67.58; H, 5.67; N, 9.85; S, 11.27.

7d: yield 92%, mp 248–250 °C. ^{1}H NMR, δ: 7.55 (d, 1H, *J* 8.0 Hz), 7.34 (d, 1H, *J* 8.0 Hz), 7.20 (m, 2H), 6.95 (d, 1H, *J* 8.0 Hz), 6.75 (s, 1H), 6.44 (d, 1H, *J* 8.1 Hz), 4.85 (s, 2H), 4.55 (t, 1H), 2.10 (m, 1H), 1.90–1.40 (m, 7H). Found (%): C, 69.58; H, 5.84; N, 9.05; S, 10.34. Calc. for $C_{18}H_{18}N_2OS$ (%): C, 69.65; H, 5.84; N, 9.02; S, 10.33.

7e: yield 78%, mp 215–217 °C. ^{1}H NMR, δ: 7.65 (d, 1H, *J* 8.0 Hz), 7.40 (d, 1H, *J* 8.0 Hz), 7.35 (m, 2H), 7.10 (d, 1H, *J* 8.0 Hz), 6.70 (s, 1H), 6.55 (d, 1H, *J* 8.0 Hz), 5.20 (s, 2H), 3.30 (m, 1H), 1.20 (m, 1H), 0.70 (m, 2H), 0.05 (m, 1H). Found (%): C, 67.99; H, 5.00; N, 9.95; S, 11.37. Calc. for $C_{16}H_{14}N_2OS$ (%): C, 68.06; H, 5.00; N, 9.92; S, 11.35.

†† A mixture of anhydrous dioxane (3 ml), a carboxylic acid (0.0011 mol) and carbonyldiimidazole (CDI) (0.18 g, 0.0011 mol) was stirred for 1 h at 50 °C. After that, compound **7a–e** (0.001 mol) was added, and the mixture was stirred for 5 h at 100 °C. The mixture was cooled and poured into a solution of sodium carbonate. The precipitate was filtered off, washed with water and recrystallised from an ethanol–DMF mixture.

8a: yield 80%, mp 171–173 °C. ^{1}H NMR, δ: 10.05 (s, 1H), 8.65 (s, 1H), 7.92 (s, 1H), 7.75 (s, 1H), 7.60 (d, 2H, *J* 8.0 Hz), 7.49 (d, 1H, *J* 8.1 Hz), 7.42 (d, 1H, *J* 8.0 Hz), 7.30 (m, 3H), 7.05 (t, 1H), 4.00 (t, 2H), 3.48 (s, 3H). Found (%): C, 59.48; H, 4.05; N, 9.96; S, 15.16. Calc. for $C_{21}H_{17}N_3O_3S_2$ (%): C, 59.56; H, 4.05; N, 9.92; S, 15.14.

8b: yield 72%, mp 257–259 °C. ^{1}H NMR, δ: 10.22 (s, 1H), 8.10 (s, 1H), 8.00 (m, 3H), 7.88 (d, 1H, *J* 8.1 Hz), 7.57 (d, 1H, *J* 8.0 Hz), 7.40 (d, 1H, *J* 8.1 Hz), 7.32 (d, 1H, *J* 8.0 Hz), 7.25 (t, 2H), 4.52 (dd, 1H), 3.65 (dd, 1H), 1.25 (t, 3H). Found (%): C, 63.66; H, 4.42; N, 9.71; S, 7.41. Calc. for $C_{23}H_{19}N_3O_4S$ (%): C, 63.73; H, 4.42; N, 9.69; S, 7.40.

8c: yield 65%, mp 208–210 °C. ^{1}H NMR, δ: 9.80 (s, 1H), 7.85 (s, 1H), 7.80 (s, 3H), 7.52 (d, 1H, *J* 8.0 Hz), 7.45 (m, 5H), 7.26 (m, 3H), 4.50 (m, 1H), 3.54 (d, 2H, *J* 6.2 Hz), 3.42 (m, 1H), 1.55 (m, 2H), 0.90 (t, 3H). Found (%): C, 59.81; H, 4.82; N, 8.75; S, 13.33. Calc. for $C_{24}H_{23}N_3O_4S_2$ (%): C, 59.86; H, 4.81; N, 8.73; S, 13.32.

8d: yield 58%, mp 103–105 °C. ^{1}H NMR, δ: 10.00 (s, 1H), 8.10 (s, 1H), 7.80 (d, 1H, *J* 8.1 Hz), 7.65 (s, 1H), 7.60 (d, 1H, *J* 8.2 Hz), 7.40 (d, 1H, *J* 8.0 Hz), 7.20 (m, 4H), 6.50 (s, 1H), 4.50 (t, 1H), 2.10 (m, 2H), 1.95 (m, 2H), 1.80 (m, 2H), 1.60 (m, 2H). Found (%): C, 68.26; H, 4.99; N, 6.89; S, 7.94. Calc. for $C_{23}H_{20}N_2O_3S$ (%): C, 68.30; H, 4.98; N, 6.93; S, 7.93.

8e: yield 50%, mp > 300 °C. ^{1}H NMR, δ: 10.30 (s, 1H), 8.70 (d, 2H, *J* 8.1 Hz), 8.05 (s, 1H), 7.81 (d, 1H, *J* 7.9 Hz), 7.75 (d, 2H, *J* 8.1 Hz), 7.70 (d, 1H, *J* 8.2 Hz), 7.45 (t, 1H), 7.38 (d, 1H, *J* 8.1 Hz), 7.30 (t, 2H), 3.35 (m, 1H), 1.20 (m, 1H), 0.80 (m, 2H), 0.20 (m, 1H). Found (%): C, 68.12; H, 4.43; N, 10.72; S, 8.28. Calc. for $C_{22}H_{17}N_3O_2S$ (%): C, 68.20; H, 4.42; N, 10.85; S, 8.27.