

Denitrocyclisation in the synthesis of dibenzothiazepinones

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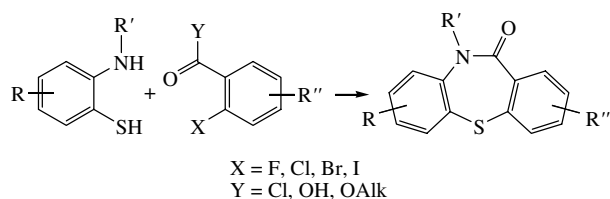
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A new method has been elaborated for the synthesis of new compounds of the dibenzothiazepine series by intramolecular aromatic substitution of the nitro group.

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,



Scheme 1

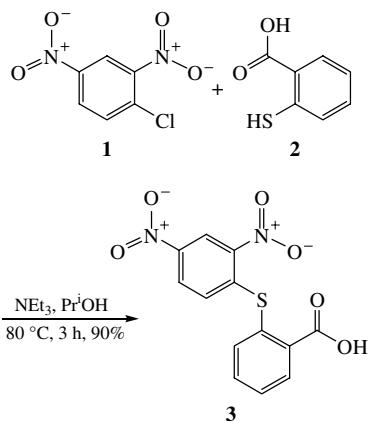
serves as the main reagent in the synthesis. We used 2,4-dinitrochlorobenzene **1** to obtain dibenzothiazepines containing a nitro group, which was then converted into an amino group.

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).[‡]

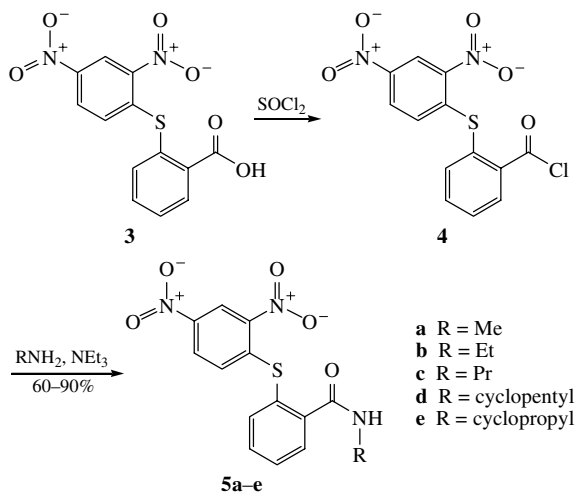
[†] ¹H NMR spectra of 5% solutions in [2H₆]DMSO with TMS as an internal standard were recorded on a Bruker DPX-300 instrument.

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. ¹H 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 C₁₃H₈N₂O₆S (%): 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

‡ 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.

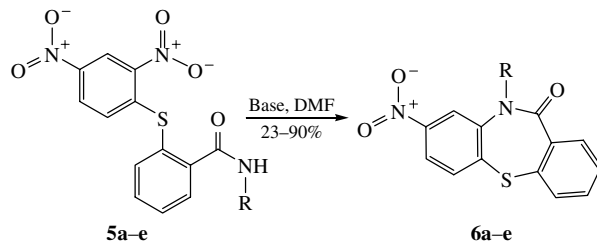
5a: yield 79%, mp 174–176 °C. ¹H NMR, δ: 8.95 (s, 1H), 8.20 (m, 2H), 7.60 (m, 4H), 7.00 (d, 1H, *J* 8.1 Hz), 2.70 (s, 3H). Found (%): C, 50.37; H, 3.33; N, 12.65; S, 9.63. Calc. for C₁₄H₁₁N₃O₅S (%): C, 50.45; H, 3.33; N, 12.61; S, 9.62.

5b: yield 82%, mp 143–145 °C. ¹H 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 C₁₅H₁₃N₃O₅S (%): C, 51.87; H, 3.77; N, 12.10; S, 9.23.

5c: yield 86%, mp 93–95 °C. ¹H 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 C₁₆H₁₅N₃O₅S (%): C, 53.18; H, 4.18; N, 11.63; S, 8.87.

5d: yield 90%, mp 140–142 °C. ¹H 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 C₁₈H₁₇N₃O₅S (%): C, 55.80; H, 4.42; N, 10.85; S, 8.28.

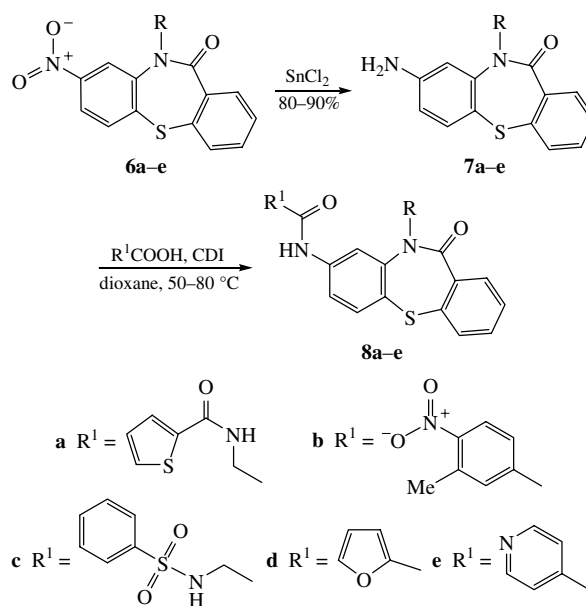
5e: yield 60%, mp 131–133 °C. ¹H NMR, δ: 8.94 (s, 1H), 8.38 (d, 1H, *J* 8.5 Hz), 8.19 (d, 1H, *J* 8.1 Hz), 7.60 (m, 4H), 7.00 (d, 1H, *J* 8.0 Hz), 2.70 (m, 1H), 0.62 (m, 2H), 0.40 (m, 2H). Found (%): C, 53.43; H, 3.65; N, 11.67; S, 8.93. Calc. for C₁₆H₁₃N₃O₅S (%): C, 53.48; H, 3.65; N, 11.69; S, 8.92.



Scheme 4 Reagents and conditions: i, 0–20 °C, 2 h, R = Me, Base = NaH (80%), NaNH₂ (23%), KOBu^t (88%); ii, 120 °C, 5 h, R = Me, Base = K₂CO₃ (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-nitro-dibenzothiazepines **6a–e** to corresponding amino **7a–e**[¶] and



Scheme 5

§ 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. ¹H 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 C₁₄H₁₀N₂O₃S (%): C, 58.73; H, 3.52; N, 9.78; S, 11.20.

6b: yield 85%, mp 119–121 °C. ¹H 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 C₁₅H₁₂N₂O₃S (%): C, 59.99; H, 4.03; N, 9.33; S, 10.67.

6c: yield 80%, mp 117–119 °C. ¹H 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 C₁₆H₁₄N₂O₃S (%): C, 61.13; H, 4.49; N, 8.91; S, 10.20.

6d: yield 87%, mp 157–159 °C. ¹H 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 C₁₈H₁₆N₂O₃S (%): C, 63.51; H, 4.74; N, 8.23; S, 9.42.

6e: yield 82%, mp 153–155 °C. ¹H 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 C₁₆H₁₂N₂O₃S (%): 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).

References

- 1 K. D. Hargrave, G. Schmidt, W. Engel and K. Schromm, *European Patent*, 419861, 1991.
- 2 R. H. Nicol, M. J. Slater and S. T. Horgson, *US Patent*, 5607929, 1997.

[†] 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. ¹H 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 C₁₄H₁₂N₂OS (%): C, 65.60; H, 4.72; N, 10.93; S, 12.51.

7b: yield 84%, mp 181–183 °C. ¹H 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 C₁₅H₁₄N₂OS (%): C, 66.64; H, 5.22; N, 10.36; S, 11.86.

7c: yield 82%, mp 172–174 °C. ¹H 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 C₁₆H₁₆N₂OS (%): C, 67.58; H, 5.67; N, 9.85; S, 11.27.

7d: yield 92%, mp 248–250 °C. ¹H 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 C₁₈H₁₈N₂OS (%): C, 69.65; H, 5.84; N, 9.02; S, 10.33.

7e: yield 78%, mp 215–217 °C. ¹H 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 C₁₆H₁₄N₂OS (%): C, 68.06; H, 5.00; N, 9.92; S, 11.35.

³ R. Pauwls, *Nature*, 1990, **343**, 470.

⁴ S. Radl, *Adv. Heterocycl. Chem.*, 2002, **83**, 189.

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^{††} 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. ¹H 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 C₂₁H₁₇N₃O₃S₂ (%): C, 59.56; H, 4.05; N, 9.92; S, 15.14.

8b: yield 72%, mp 257–259 °C. ¹H 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 C₂₃H₁₉N₃O₄S (%): C, 63.73; H, 4.42; N, 9.69; S, 7.40.

8c: yield 65%, mp 208–210 °C. ¹H 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 C₂₄H₂₃N₃O₄S₂ (%): C, 59.86; H, 4.81; N, 8.73; S, 13.32.

8d: yield 58%, mp 103–105 °C. ¹H 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 C₂₃H₂₀N₂O₃S (%): C, 68.30; H, 4.98; N, 6.93; S, 7.93.

8e: yield 50%, mp > 300 °C. ¹H 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 C₂₂H₁₇N₃O₂S (%): C, 68.20; H, 4.42; N, 10.85; S, 8.27.