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Mendeleev Commun., 2008, **18**, 281–283
Mendeleev Communications

Synthesis of dibenzo[*b*,*f*][1,4]oxazepin-11(10*H*)-one and pyrido[2,3-*b*][1,4]benzoxazepin-10(11*H*)-one compounds based on *o*-nitrochloro derivatives of benzene and pyridine

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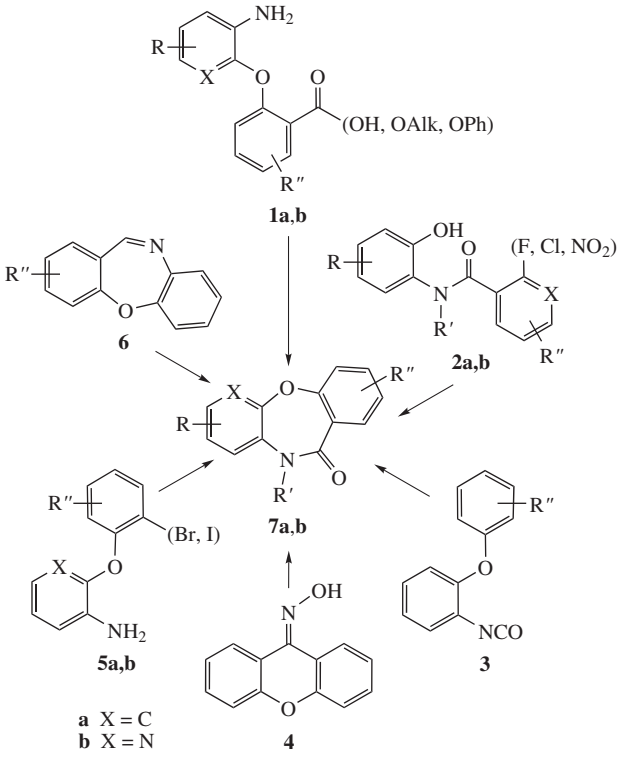
DOI: 10.1016/j.mencom.2008.09.019

A new approach to the construction of tricyclic dibenzo[*b*,*f*][1,4]oxazepin-11(10*H*)-one and pyrido[2,3-*b*][1,4]benzoxazepin-10(11*H*)-one systems based on N-substituted salicylamides and *o*-nitrochloro derivatives of benzene and pyridine has been developed.

The pharmacological properties of dibenzo[*b*,*f*][1,4]oxazepin-11(10*H*)-one derivatives and their use in medical practices have been reported.[1–6]

The synthesis of derivatives **7a** was described in 1934; it involved the thermal cyclisation of 2-(2-aminophenoxy)benzoic acid **1a** (Scheme 1).[7–9] This synthesis can be performed using different[10–13] esters **1a**,**b**, and the cyclisation can be carried out in different solvents.[14–16] Another method for constructing the heterocyclic system of compounds **7a**,**b** involves intramolecular aromatic substitution in 2-(*o*-halobenzamido)phenols,[2,4,17–19] 2-(*o*-nitrobenzamido)phenols **2a**[20,21] or 2-halo-*N*-(2-hydroxyphenyl)nicotinamides **2b**.[4] Intramolecular acylation of 1-isocyanato-2-phenoxybenzenes **3** gives dibenzo[*b*,*f*][1,4]oxazepin-11(10*H*)-ones **7a** in good yields.[17,22,23] Another less popular method involves the heating of xanthen-9-one oximes **4** with phosphorus pentachloride[17] or polyphosphoric acid.[24] This results in a dibenzoxazepine system *via* Beckmann rearrangement. Note that the synthesis of benzoxazepinones **7a**,**b** based on the reaction of 2-(2-halophenoxy)phenylamines **5a** and 2-(2-halophenoxy)pyridine-3-amines **5b** with carbon monoxide under pressure in the presence of palladium catalysts.[25] This method involves the oxidation of dibenzo[*b*,*f*][1,4]oxazepines **6**. Sodium dichromate in acetic acid as the oxidant gives derivatives **7a**,[18] whereas hydrogen peroxide gives a mixture of products including target dibenzoxazepinone **7a**.[26]



Scheme 1

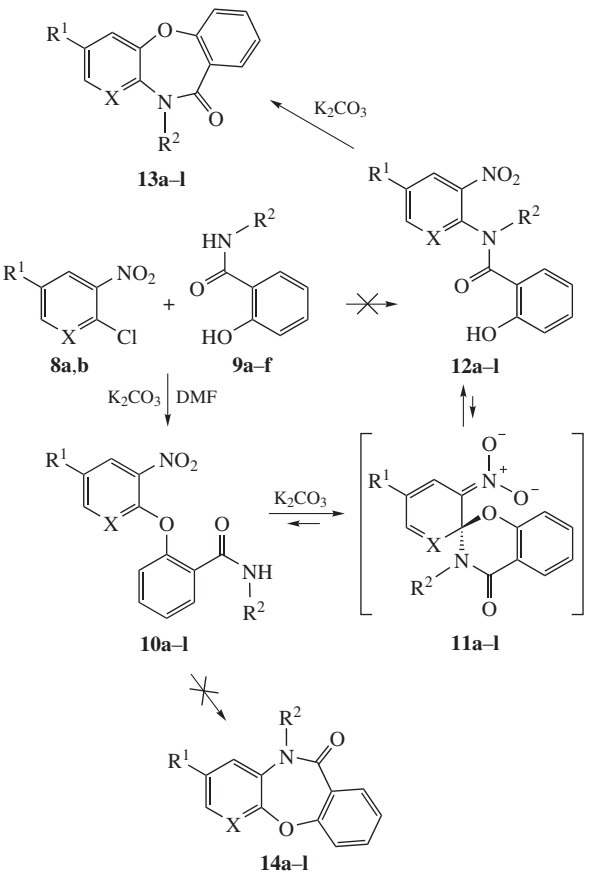
We found that the use of intramolecular nucleophilic aromatic substitution of a nitro group (denitrocyclisation[27]) for constructing a tricyclic system is a promising method for the synthesis of dibenzo[*b*,*f*][1,4]thiazepin-11(10*H*)-one derivatives.[28–30] A distinctive feature of this approach is that not only the phenol nucleophilic centre but also the amide one are involved in the reaction.

We used this approach to synthesise dibenzo[*b*,*f*][1,4]oxazepin-11(10*H*)-one derivatives **13a–f** and hitherto unknown pyrido[2,3-*b*]-[1,4]benzoxazepin-10(11*H*)-one derivatives **13g–l** (Scheme 2). We used 4-chloro-3-nitrobenzonitrile **8a** and 2-chloro-3-nitropyridine **8b** as the substrates and N-alkyl- and N-aryl-substituted salycilamides **9** as the reagents. The reaction was carried out in DMF in the presence of a base. If strong bases such as sodium hydride, sodium amide or potassium *tert*-butoxide 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, *e.g.*, Chichibabin amination. The use of potassium carbonate as the deprotonating agent also resulted in denitrocyclisation at temperatures of ≥ 80 °C. The use of potassium carbonate was beneficial as it became unnecessary to use anhydrous DMF and the yields of the target products were high.†

Hypothetically, the first step of the reaction of compounds **8** and **9** is either replacement of the chlorine atom with the phenol oxygen atom to give intermediate compounds **10** or replacement of the chlorine atom with an amide reaction centre to give intermediate compounds **12**.

It was found using ^{1}H NMR spectroscopy‡ that, in the reaction of compounds **8a** and **9a**, the signals of the phenol proton (δ 13.7 ppm) and amide proton (δ 8.5 ppm) in compound **9a** were no longer observed even 30 s after the start of the reaction. Simultaneously, the signal of the amide proton in compound **10a**§ was recorded in the region of δ 9.5–10.0 ppm, which then decreased to zero in the course of the reaction. Obviously, this means that in this case, the reaction of compounds **8a** and **9a** initially gives not amide **12a** but diphenyl ether **10a**, whose amide reaction centre can subsequently be involved in denitrocyclisation to yield **13a** or **14a**.

In the reaction with compound **8b** as the substrate, the course of the reaction was determined using model experiments (Scheme 3). We had to do so because, unlike in the first reaction, we failed to isolate intermediate compounds **10g–l** or **12g–l** from the reaction mixture, or obtain them in a pure form, for the identification and assignment of signals. The reaction of compound **8b** with 2-hydroxy-*N*,*N*-dimethylbenzamide **15** in DMF in the presence of potassium carbonate gave *N*,*N*-dimethyl-2-(3-nitropyridin-2-yloxy)benzamide **16** in a high yield.¶ On the other hand, we did not detect a reaction of compound **8b** with 2-methoxy-*N*-methylbenzamide **17** even at 110 °C. Data of model experiments suggest that the reaction of **8b** with compounds **9** occurs by the same pathway as in the case of **8a**.



8: **a** X = C, R^1 = CN; **b** X = N, R^1 = H

9: **a** R^2 = Me; **b** R^2 = Et; **c** R^2 = Pr; **d** R^2 = Ph; **e** R^2 = *p*-MeC_6H_4; **f** R^2 = *p*-ClC_6H_4

10–14: **a** X = C, R^1 = CN, R^2 = Me; **b** X = C, R^1 = CN, R^2 = Et; **c** X = C, R^1 = CN, R^2 = Pr; **d** X = C, R^1 = CN, R^2 = Ph; **e** X = C, R^1 = CN, R^2 = *p*-MeC_6H_4; **f** X = C, R^1 = CN, R^2 = *p*-ClC_6H_4; **g** X = N, R^1 = H, R^2 = Me; **h** X = N, R^1 = H, R^2 = Et; **i** X = N, R^1 = H, R^2 = Pr; **j** X = N, R^1 = H, R^2 = Ph; **k** X = N, R^1 = H, R^2 = *p*-MeC_6H_4; **l** X = N, R^1 = H, R^2 = *p*-ClC_6H_4

Scheme 2

† ^{1}H NMR spectra and two-dimensional correlation spectra ^{1}H–^{1}H NOESY of 5% solutions of the samples in [$^2H_6$]DMSO were recorded using a Bruker MSL-300 spectrometer.

General procedure for the synthesis of **13a–l**. A mixture of compound **8** (0.10 mol), compound **9** (0.10 mol) and anhydrous K_2CO_3 (34.5 g, 0.25 mol) in DMF (150 ml) was stirred for 4 h at 75–80 °C, cooled and poured into water. The precipitate formed was filtered off and recrystallised from ethanol. Yield, 65–80%.

13a: yield 80%, mp 147–149 °C. ^{1}H NMR, δ: 7.86 (s, 1H), 7.76 (d, 1H, *J* 8.8 Hz), 7.68 (d, 1H, *J* 8.8 Hz), 7.59 (t, 2H), 7.34 (m, 2H), 3.54 (s, 3H). Found (%): C, 71.93; H, 4.03; N, 11.16. Calc. for $C_{15}H_{10}N_2O_2$ (%): C, 71.99; H, 4.03; N, 11.19.

13b: yield 79%, mp 155–158 °C. ^{1}H NMR, δ: 7.88 (s, 1H), 7.72 (d, 1H, *J* 8.1 Hz), 7.68 (m, 2H), 7.58 (t, 1H), 7.34 (m, 2H), 4.22 (dd, 2H), 1.60 (m, 3H). Found (%): C, 72.50; H, 4.59; N, 10.63. Calc. for $C_{16}H_{12}N_2O_2$ (%): C, 72.71; H, 4.58; N, 10.60.

13c: yield 70%, mp 134–137 °C. ^{1}H NMR, δ: 7.88 (s, 1H), 7.82 (d, 1H, *J* 8.0 Hz), 7.68 (m, 2H), 7.58 (t, 1H), 7.34 (m, 2H), 4.22 (dd, 2H), 1.66 (m, 2H), 0.98 (m, 3H). Found (%): C, 73.20; H, 5.08; N, 10.09. Calc. for $C_{17}H_{14}N_2O_2$ (%): C, 73.37; H, 5.07; N, 10.07.

13d: yield 65%, mp 151–154 °C. ^{1}H NMR, δ: 8.58 (s, 1H), 8.18 (m, 2H), 7.92 (m, 2H), 7.72 (m, 2H), 7.52 (m, 4H), 7.30 (d, 1H, *J* 8.8 Hz). Found (%): C, 76.71; H, 3.88; N, 9.01. Calc. for $C_{20}H_{12}N_2O_2$ (%): C, 76.91; H, 3.87; N, 8.97.

13e: yield 80%, mp 169–172 °C. ^{1}H NMR, δ: 7.91 (s, 1H), 7.73–7.85 (m, 4H), 7.60 (d, 1H, *J* 8.1 Hz), 7.52 (m, 2H), 70.31 (m, 2H), 7.24 (t, 1H), 2.54 (s, 3H). Found (%): C, 77.15; H, 4.33; N, 8.62. Calc. for $C_{21}H_{14}N_2O_2$ (%): C, 77.29; H, 4.32; N, 8.58.

13f: yield 85%, mp 147–150 °C. ^{1}H NMR, δ: 7.95 (s, 1H), 7.80 (m, 2H), 7.54–7.71 (m, 7H), 7.32 (t, 1H). Found (%): C, 69.08; H, 3.20; N, 8.12. Calc. for $C_{20}H_{11}ClN_2O_2$ (%): C, 69.27; H, 3.20; N, 8.08.

13g: yield 65%, mp 113–116 °C. ^{1}H NMR, δ: 8.29 (d, 1H, *J* 5.0 Hz), 7.76 (m, 2H), 7.57 (t, 1H), 7.23–7.34 (m, 3H), 3.56 (s, 3H). Found (%): C, 68.81; H, 4.46; N, 12.44. Calc. for $C_{13}H_{10}N_2O_2$ (%): C, 69.02; H, 4.46; N, 12.38.

13h: yield 65%, mp 61–64 °C. ^{1}H NMR, δ: 8.28 (d, 1H, *J* 4.4 Hz), 7.5 (m, 2H), 7.56 (t, 1H), 7.21–7.32 (m, 3H), 4.23 (dd, 2H), 1.34 (t, 3H). Found (%): C, 69.78; H, 5.04; N, 11.72. Calc. for $C_{14}H_{12}N_2O_2$ (%): C, 69.99; H, 5.03; N, 11.66.

13i: yield 75%, mp 83–86 °C. ^{1}H NMR, δ: 8.29 (d, 1H, *J* 3.7 Hz), 7.75 (m, 2H), 7.55 (t, 1H), 7.22–7.32 (m, 3H), 4.16 (t, 2H), 1.68 (m, 2H), 0.89 (t, 3H). Found (%): C, 70.64; H, 5.56; N, 11.07. Calc. for $C_{15}H_{14}N_2O_2$ (%): C, 70.85; H, 5.55; N, 11.02.

13j: yield 80%, mp 145–148 °C. ^{1}H NMR, δ: 8.10 (d, 1H, *J* 4.5 Hz), 7.83 (m, 2H), 7.60 (t, 1H), 7.20–7.42 (m, 8H). Found (%): C, 74.76; H, 4.20; N, 9.77. Calc. for $C_{18}H_{12}N_2O_2$ (%): C, 74.99; H, 4.20; N, 9.72.

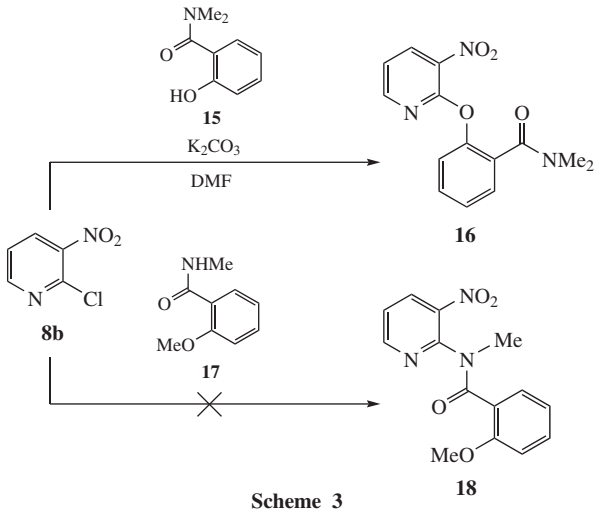
13k: yield 85%, mp 151–154 °C. ^{1}H NMR, δ: 8.11 (d, 1H, *J* 4.8 Hz), 7.84 (m, 2H), 7.65 (t, 1H), 7.37 (m, 2H), 7.27 (m, 5H), 2.40 (s, 3H). Found (%): C, 75.25; H, 4.67; N, 9.29. Calc. for $C_{19}H_{14}N_2O_2$ (%): C, 75.48; H, 4.67; N, 9.27.

13l: yield 90%, mp 132–135 °C. ^{1}H NMR, δ: 8.11 (d, 1H, *J* 4 Hz), 7.85 (m, 2H), 7.66 (t, 1H), 7.20–7.78 (m, 7H). Found (%): C, 66.85; H, 3.44; N, 8.71. Calc. for $C_{18}H_{11}ClN_2O_2$ (%): C, 66.99; H, 3.44; N, 8.68.

‡ *Analytical control technique using ^{1}H NMR spectroscopy.* Compounds **8a**,**b** (0.02 mol) and **9a** (0.02 mol) and anhydrous K_2CO_3 (0.06 mol) were added to [$^2H_6$]DMSO (5 ml); the reaction mixture was stirred at 75 °C and samples were taken at a specified time.

§ *Synthesis of model compound* **10a** *for identification and assignment of signals.* A mixture of compound **8a** (0.05 mol), methyl salicylate (0.05 mol) and anhydrous K_2CO_3 (0.10 mol) in DMF (150 ml) was stirred for 3 h at 80 °C, then the reaction mixture was cooled and poured into water. The precipitate formed was filtered off and recrystallised from ethanol. The resulting ester was hydrolysed at 20 °C for 3 h in water–ethanol using an equimolar amount of sodium hydroxide. Acidification of the reaction mixture with concentrated hydrochloric acid to pH 1 gave the pure acid. Amide **10a** was synthesised by heating a mixture of phenoxysalicylic acid (0.10 mol), methylamine (0.10 mol) and *N*,*N*-carbonyldiimidazole (0.10 mol) in dioxane at 50 °C for 3 h. Yield, 53%, mp 128–131 °C. ^{1}H NMR, δ: 9.43 (s, 1H), 8.54 (m, 2H), 7.45 (m, 5H), 2.64 (d, 3H).

Obviously, the amide group in salicylamides **9** cannot serve as the nucleophilic reaction centre at the first stage of the process in question, and compounds **10a–l** are intermediate products on the pathway that leads to the target tricyclic systems.



Scheme 3

^{1}H–^{1}H NOESY spectrum of the end product obtained from compound **8a**†† contains a cross-peak that characterises the interaction of NMe protons (δ 3.5 ppm) with one aromatic proton (the proton at C^9, δ 7.68 ppm). The signal of this proton is a doublet with J 8.8 Hz, which characterises its *ortho*-interaction with another proton (the proton at C^8, δ 7.76 ppm); this is also observed as a cross peak in the NOESY spectrum.

^{1}H–^{1}H NOESY spectrum of the end product obtained from compound **8b**†† contains a cross-peak in the region characterising the interaction of the protons in the NMe group (δ 3.56 ppm) with an aromatic proton in the pyridinium ring (the proton at C^3, δ 7.76 ppm).

2D correlation spectra ^{1}H–^{1}H NOESY provide more detailed information on denitrocyclisation products. They do not match structures **14** that can result from direct denitrocyclisation of compounds **10**. The spectral data are in full agreement with structures **13**, which are presumably formed due to the Smiles rearrangement[31–33] preceding the intramolecular aromatic substitution of the nitro group and occurring *via* intermediates **11** and **12** (Scheme 2).

Thus, this study has shown that the first stage of the process of interest involves the hydroxy group as the nucleophilic reaction centre in salicylamides. The formation of the target tricyclic systems involves binuclear diphenyl ethers or phenoxypyridines as intermediates. The intramolecular aromatic substitution of the nitro group is preceded by a Smiles rearrangement. An undeniable advantage of the approach to the construction of dibenzo[*b*,*f*][1,4]oxazepin-11(10*H*)-one and pyrido[2,3-*b*][1,4]-benzoxazepin-10(11*H*)-one systems is that diverse substituents can be introduced at the nitrogen atom before the tricyclic system is formed and that a wide range of compounds belonging to these classes can be obtained in high yields.

¶ A mixture of compound **8b** (0.05 mol), compound **14** (0.05 mol) and anhydrous K_2CO_3 (0.12 mol) in DMF (150 ml) was stirred for 4 h at 75–80 °C, then the reaction mixture was cooled and poured into water. The precipitate formed was filtered off and recrystallised from ethanol to give compound **16**. Yield 85%; mp 110–113 °C. ^{1}H NMR, δ: 7.81 (s, 1H), 7.65 (d, 1H, J 8.8 Hz), 7.54 (d, 1H, J 8.8 Hz), 7.49 (t, 2H), 7.34 (m, 2H), 3.45 (s, 6H).

†† For ^{1}H–^{1}H NOESY spectra of the end products obtained from compounds **8a** and **8b**, see Online Supplementary Materials.

This study was supported by the Federal Agency for Science and Innovations (state contract no. 02.527.11.9002).

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2008.09.019.

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Received: 28th February 2008; Com. 08/3089