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Stereoselective synthesis of N-unsubstituted pyrazolidines from 3-nitro-2-trichloromethyl-2*H*-chromenes and hydrazine hydrate

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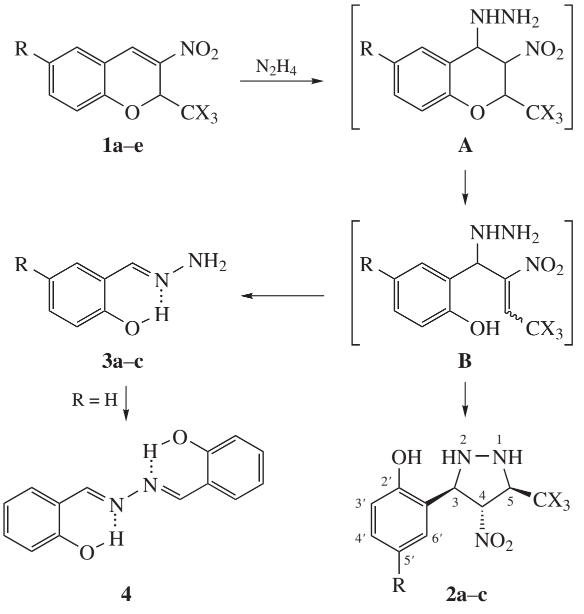
The reaction of 3-nitro-2-trichloromethyl-2*H*-chromenes with hydrazine hydrate in ethanol at room temperature results in 3,4-*trans*, 4,5-*trans*-3-(2-hydroxyaryl)-4-nitro-5-trichloromethylpyrazolidines in 56–73% yields; the structures of these compounds were established by ^{1}H NMR, 2D COSY and 2D NOESY spectra.

Unlike pyrazoles and pyrazolines whose synthetic methods are well developed,[1] pyrazolidines are not so readily accessible. They were previously obtained by reduction of pyrazolines[2] or pyrazolium salts[3,4] and by the reactions of hydrazine with 1,3-dibromides[2,5] or phenylhydrazones with electron-deficient alkenes.[6]

In a study of the reactivity of 3-nitro-2-trihalomethyl-2*H*-chromenes **1** synthesised by tandem condensation of salicylic aldehydes with 1-nitro-3,3,3-trihalopropenes,[7] we found that the reaction of these compounds with hydrazine hydrate did not end at the stage of nucleophilic addition to C(4), as was the case with a number of S-, N- and C-mononucleophiles,[8,9] but involved recyclisation of the pyrane ring to the pyrazolidine ring.

The reaction of 3-nitro-2-trichloromethyl-2*H*-chromenes **1a**–**c** with an equimolar amount of 60% hydrazine hydrate in ethanol at room temperature resulted in pyrazolidines **2a**–**c** each as a single, most thermodynamically stable 3,4-*trans*, 4,5-*trans*-diastereomer in 56–73% yields.† As far as we know, no functionalised N-unsubstituted pyrazolidines have been reported before. Phenylhydrazine does not react with chromenes **1a**,**c** under these conditions. Products **2a**–**c** are white high-melting powders stable in storage. Note that pyrazolidine **2b** is not oxidised in air when kept in a chloroform solution for five days, and its configuration does not change on refluxing in methanol in the presence of K_2CO_3. A possible reaction mecha-



a R = H, X = Cl
b R = MeO, X = Cl
c R = Br, X = Cl
d R = H, X = F
e R = MeO, X = F

Scheme 1

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† *General procedure for the synthesis of pyrazolidines* **2**. A solution of 60% hydrazine hydrate (0.08 g, 1.0 mmol) in 2 ml of ethanol was added to a suspension of corresponding nitrochromene **1** (1.0 mmol) in 5 ml of ethanol. The reaction mixture was kept for 24 h at ~20 °C. After that, in the case of compound **2a**, the solvent was evaporated to half of its initial volume and 5 ml of H_2O was added. The precipitate formed was filtered off, dissolved in ethanol, precipitated with water and dried in air. In the case of compounds **2b**,**c**, the solvent was evaporated to dryness and the precipitate was treated with a CH_2Cl_2–hexane mixture (2:1) in order to remove hydrazones **3b**,**c**.

3-(2-Hydroxyphenyl)-4-nitro-5-trichloromethylpyrazolidine **2a**: yield 73%, mp 183–184 °C (decomp.), white powder. ^{1}H NMR (400 MHz, $[^2H_6]$DMSO) δ: 4.67 (dd, 1H, H-3, $J_{3,2}$ 13.2 Hz, $J_{3,4}$ 8.8 Hz), 4.98 (dd, 1H, H-5, $J_{5,1}$ 9.0 Hz, $J_{5,4}$ 5.8 Hz), 5.07 (dd, 1H, H-2, $J_{2,3}$ 13.2 Hz, $J_{2,1}$ 10.9 Hz), 5.57 (dd, 1H, H-4, $J_{4,3}$ 8.8 Hz, $J_{4,5}$ 5.8 Hz), 6.35 (dd, 1H, H-1, $J_{1,2}$ 10.9 Hz, $J_{1,5}$ 9.0 Hz), 6.81 (t, 1H, H-5′, ^3J 7.5 Hz), 6.88 (d, 1H, H-3′, ^3J 7.9 Hz), 7.21 (td, 1H, H-4′, ^3J 7.6 Hz, ^4J 1.5 Hz), 7.24 (br. d, 1H, H-6′, ^3J 7.5 Hz), 10.23 (s, 1H, OH). IR (KBr, ν/cm^{-1}): 3361, 3288, 1634, 1615, 1557, 1482, 1461, 1420, 1370. Found (%): C, 36.87; H, 3.03; N, 12.86. Calc. for $C_{10}H_{10}Cl_3N_3O_3$ (%): C, 36.78; H 3.09; N, 12.87.

3-(2-Hydroxy-5-methoxyphenyl)-4-nitro-5-trichloromethylpyrazolidine **2b**: yield 56%, mp 173–174 °C (decomp.), white powder. ^{1}H NMR (400 MHz, $[^2H_6]$DMSO) δ: 3.67 (s, 3H, MeO), 4.65 (dd, 1H, H-3, $J_{3,2}$ 13.2 Hz, $J_{3,4}$ 8.8 Hz), 4.98 (dd, 1H, H-5, $J_{5,1}$ 9.0 Hz, $J_{5,4}$ 5.8 Hz), 5.11 (dd, 1H, H-2, $J_{2,3}$ 13.2 Hz, $J_{2,1}$ 10.9 Hz), 5.56 (dd, 1H, H-4, $J_{4,3}$ 8.8 Hz, $J_{4,5}$ 5.8 Hz), 6.33 (dd, 1H, H-1, $J_{1,2}$ 10.9 Hz, $J_{1,5}$ 9.0 Hz), 6.80–6.84 (m, 3H, H-3′, H-4′, H-6′), 9.73 (s, 1H, OH). IR (KBr, ν/cm^{-1}): 3356, 3298, 3258, 1613, 1554, 1518, 1494, 1456, 1437, 1368. Found (%): C, 36.98; H, 3.38; N, 11.61. Calc. for $C_{11}H_{12}Cl_3N_3O_4$ (%): C, 37.05; H 3.39; N, 11.78.

3-(5-Bromo-2-hydroxyphenyl)-4-nitro-5-trichloromethylpyrazolidine **2c**: yield 70%, mp 172–173 °C (decomp.), white powder. ^{1}H NMR (400 MHz, $[^2H_6]$DMSO) δ: 4.67 (dd, 1H, H-3, $J_{3,2}$ 13.0 Hz, $J_{3,4}$ 8.8 Hz), 4.99 (dd, 1H, H-5, $J_{5,1}$ 9.0 Hz, $J_{5,4}$ 5.8 Hz), 5.14 (dd, 1H, H-2, $J_{2,3}$ 13.0 Hz, $J_{2,1}$ 10.8 Hz), 5.53 (dd, 1H, H-4, $J_{4,3}$ 8.8 Hz, $J_{4,5}$ 5.8 Hz), 6.33 (dd, 1H, H-1, $J_{1,2}$ 10.8 Hz, $J_{1,5}$ 9.0 Hz), 6.83 (d, 1H, H-3′, ^3J 8.6 Hz), 7.38 (dd, 1H, H-4′, ^3J 8.6 Hz, ^4J 2.5 Hz), 7.52 (d, 1H, H-6′, ^4J 2.5 Hz), 10.58 (s, 1H, OH). IR (KBr, ν/cm^{-1}): 3356, 3285, 1626, 1557, 1481, 1438, 1415, 1363. Found (%): C, 29.65; H, 2.21; N, 10.30. Calc. for $C_{10}H_9BrCl_3N_3O_3$ (%): C, 29.62; H, 2.24; N, 10.36.

nism involves the addition of a hydrazine molecule to C(4) (intermediate **A**) followed by opening of the pyran ring and formation of intermediate **B**, which is closed to give a pyrazolidine ring as a result of an intramolecular attack of the primary amino group at the activated double bond of the nitroalkene fragment (Scheme 1).

As a side reaction, intermediate **B** is decomposed to give hydrazone **3**, which becomes the predominant product if the amount of hydrazine is increased or if the reaction is carried out in boiling ethanol. Under these conditions, 2-trichloromethylchromenes **1a**–**c** gave hydrazones **3a**–**c** as major products;[‡] of these, compound **3a** was isolated as a mixture with azine **4** in the ratio **3a**:**4** = 3:1. The latter, probably, is the result of self-condensation of salicylic aldehyde hydrazone. The reaction of 3-nitro-2-trifluoromethyl-2*H*-chromene **1d** with hydrazine hydrate results in a similar mixture, both at room temperature and with cooling to 5 °C, whereas the reaction with chromene **1e** at ~20 °C gives hydrazone **3b** in 41% yield. Under the same conditions, 3-nitro-2-phenyl-2*H*-chromene[10] reacts ambiguously to give a hardly identifiable product mixture. It should be noted that the formation of hydrazones of salicylic aldehydes **3** was observed previously in the reaction of hydrazine hydrate with substituted 3-carbethoxycoumarins.[11]

The ^{1}H NMR spectra of pyrazolidines **2a**–**c** in [^{2}H$_6$]DMSO contain five doublets of doublets, two of which correspond to mobile protons at nitrogen atoms ($\delta_{\text{H-1}}$ 6.33–6.35, $\delta_{\text{H-2}}$ 5.07–5.14, $J_{1,2}$ 10.9 Hz, $J_{1,5}$ 9.0 Hz, $J_{2,3}$ 13.1 Hz). The signals of all protons were assigned based on the 2D COSY spectrum of pyrazolidine **2a**, while its 3,4-*trans*, 4,5-*trans* configuration was confirmed by the 2D NOESY spectrum, in which cross peaks between the H(3)-H(5) and H(4)-H(6′) protons were observed.

Thus, the conversion of 2-trichloromethylchromenes on treatment with hydrazine hydrate under mild conditions described here is the first example of recyclisation of the 2*H*-chromene system to give N-unsubstituted pyrazolidines. If the reaction is carried out under more drastic conditions or if 2-trifluoromethylchromenes are used, it gives the hydrazone of the corresponding salycilic aldehyde or its mixture with an azine as the main products.

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[‡] *Salicylic aldehyde hydrazone* **3a** (75%): ^{1}H NMR (400 MHz, CDCl$_3$) δ: 5.43 (br. s, 2H, NH$_2$), 6.86 (td, 1H, H-5, ^3J 7.5 Hz, ^4J 1.1 Hz), 6.94 (dd, 1H, H-3, ^3J 8.2 Hz, ^4J 1.1 Hz), 7.10 (dd, 1H, H-6, ^3J 7.7 Hz, ^4J 1.7 Hz), 7.21 (ddd, 1H, H-4, ^3J 8.2, 7.3 Hz, ^4J 1.7 Hz), 7.88 (s, 1H, CH=), 11.04 (s, 1H, OH). *Salicylic aldehyde azine* **4** (25%): ^{1}H NMR (400 MHz, CDCl$_3$) δ: 6.98 (td, 2H, H-5, ^3J 7.5 Hz, ^4J 1.1 Hz), 7.04 (d, 2H, H-3, ^3J 8.3 Hz), 7.36 (dd, 2H, H-6, ^3J 7.7 Hz, ^4J 1.7 Hz), 7.40 (ddd, 2H, H-4, ^3J 8.3, 7.3 Hz, ^4J 1.7 Hz), 8.72 (s, 2H, CH=), 11.39 (s, 2H, OH).

2-Hydroxy-5-methoxybenzaldehyde hydrazone **3b**: yield 41%, mp 110–112 °C (lit.,[12] mp 111–113 °C). ^{1}H NMR (400 MHz, CDCl$_3$) δ: 3.76 (s, 3H, MeO), 5.45 (br. s, 2H, NH$_2$), 6.63 (d, 1H, H-6, ^4J 2.9 Hz), 6.80 (dd, 1H, H-4, ^3J 8.9 Hz, ^4J 2.9 Hz), 6.87 (d, 1H, H-3, ^3J 8.9 Hz), 7.82 (s, 1H, CH=), 10.60 (s, 1H, OH). IR (KBr, ν/cm^{-1}): 3383, 3288, 1617, 1580, 1494, 1465.

5-Bromo-2-hydroxybenzaldehyde hydrazone **3c**: yield 78%, mp 71–72 °C (hexane–CH$_2$Cl$_2$) (lit.,[12] mp 68–70 °C). ^{1}H NMR (400 MHz, CDCl$_3$) δ: 5.52 (br. s, 2H, NH$_2$), 6.83 (d, 1H, H-3, ^3J 8.7 Hz), 7.20 (d, 1H, H-6, ^4J 2.4 Hz), 7.28 (dd, 1H, H-4, ^3J 8.7 Hz, ^4J 2.4 Hz), 7.76 (s, 1H, CH=), 11.03 (s, 1H, OH). IR (KBr, ν/cm^{-1}): 3393, 3157, 1620, 1565, 1479, 1438.

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