One-pot condensation of 2-arylpropenes with formaldehyde and ammonium chloride: the synthesis of aryl substituted pyridines and 5,7,11-trioxa-1-azatricyclo[7.3.1.0^{3,8}]tridecanes

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A mixture consisting of 2-arylpropene 1 or 2, formaldehyde and ammonium chloride condenses in a one-pot manner to yield 5,7,11-trioxa-1-azatricyclo $[7.3.1.0^{3.8}]$ tridecanes 3 or 4. In the presence of manganese dioxide the reaction leads to 4-arylpyridines 5 or 6.

It is well known¹ that the acid-catalysed reaction of 2-arylpropenes with formaldehyde and amines or ammonia leads to the formation of 4-aryl-4-hydroxypiperidines, which can be subsequently dehydrated into tetrahydropyridines (THPs). Under the Prins reaction conditions, *N*-alkyl substituted THPs can be hydroxymethylated at β -carbon atoms^{2,3} and subsequently converted into piperidinodioxanes^{4,5} and 3-oxa-7-azabicyclononanes.^{5,6} In the presence of manganese dioxide, the hydroxymethylation of THP proceeds at the α , β -carbon atoms leading to 6-oxa-2-azabicyclooctanones.⁵

Continuing our work^{3,5,7,8} towards the search of a new tetrahydropyridine reaction, we decided to study the one-pot condensation of 2-arylpropenes with ammonium chloride and an excess of formaldehyde according to the classic Prins reaction or modified by the presence of manganese dioxide. The expected novelty of this research is based on the presumption that initially formed NH-tetrahydropyridines could then be N- and C-hydroxymethylated and subsequently cyclocondensed or oxidised. Thus, a mixture containing 2-phenylpropene 1 or 2-(p-tolyl)propene 2, ammonium chloride and a 4.5-fold molar excess of formaldehyde was heated at 80 °C for 7 h. After this time, hydrochloric acid and 2.5 equiv. of formaldehyde were added and the reaction mixture was then heated at 80 °C for another 10 h (Scheme 1). After work-up of the reaction mixture, compounds 3 or 4 were obtained as oils in 47% and 34% yields, respectively, which slowly crystallised on standing.



Scheme 1 Reagents and conditions: i, 1 (or 2):CH₂O:NH₄Cl = 1:4.5:1, 80 °C, 7 h; then 0.006 equiv. of HCl (36% aqueous solution) and 2.5 equiv. of CH₂O were added, 80 °C, 10 h; ii, 1 (or 2):CH₂O:NH₄Cl = 1:4.5:1, 80 °C, 7 h; then 0.006 equiv. of HCl, 2.5 equiv. of CH₂O and 10 equiv. of MnO₂ were added, 80 °C, 7 h.

X-ray analysis of the product derived from styrene **2** (the detailed data will be reported elsewhere) showed (Figure 1) it to be 8-(*p*-tolyl)-5,7,11-trioxa-1-azatricyclo[7.3.1.0^{3,8}]tridecane **4**. The ¹H NMR spectra of compounds **3** and **4** and X-ray analysis data of compound **4** support that all three six-membered rings in these compounds adopt a chair conformation. The dioxane ring is *cis*-coupled to the piperidine ring (H-3 is in an axial position in both heterocycles and appears in the ¹H NMR spectra as a narrow unresolved multiplet with $\Delta v_{1/2} = 7.1$ Hz). Furthermore, the oxazine ring is 1,3-*cis*-diaxially coupled to the piperidine ring.

When the reaction was repeated in the presence of manganese dioxide (experiment ii, Scheme 1), 4-arylpyridines 5 or 6



Figure 1 General view and numbering of atoms of molecule 4 (X-ray data).

were obtained as the only isolated products in 32% and 27% yields, respectively.

Although not all the steps involved in the one-pot synthesis of final products **3–6** are known with certainty (conversions $1 \rightarrow A \rightarrow B$ are known), a likely sequence of cascade chemical events ($B \rightarrow C \rightarrow D \rightarrow E \rightarrow F$) can be proposed as shown in Scheme 2.

Partial support for the proposed reaction sequence of Scheme 2 is to be found in earlier work^{3,5} that refers to the aromatization



of *N*-methylTHP by action of manganese dioxide and manganese permanganate in a manner depicted by steps **B**–**D** above.

In conclusion, we observed that: (1) the one-step condensation of 2-arylpropenes with formaldehyde and ammonium chloride gives novel heterocyclic tricyclotridecanes in a stereoselective manner; and (2) in the presence of an oxidant, the Prins reaction does not take place and instead 4-arylpyridines are the stable final products.

The structures of compounds 3-6 were confirmed spectroscopically.^ \dagger

 † ¹H NMR spectra were recorded at 400 MHz, standard TMS, CDCl₃. Compounds **3** and **4** gave satisfactory elemental analyses.

8-Phenyl-5,7,11-trioxa-1-azatricyclo[7.3.1.0^{3,8}]tridecane **3**: yield 47%, mp 140–142 °C. ¹H NMR, δ: 1.3 (m, 1H, 3-H, $\Delta \nu_{1/2}$ 7.1 Hz), 3.05–3.22 (m, 3H, 2-CH₂ and 13-H), 3.45 (br. d, 1H, 13-H, ²J 11.8 Hz), 3.54 and 3.67 (br. d and dd, 1H each, 4-CH₂, ²J 11.6 Hz, ³J 2.4 Hz), 3.78 and 3.83 (br. d and dd, 2H, 10-CH₂, ²J 11.7 Hz, ³J 2.3 Hz), 3.75–3.85 (br. m, 1H, 9-H), 4.62 and 4.69 (br. d and dd, 2H, 12-CH₂, ²J 10.4 Hz, ³J 1.5 Hz), 4.71 and 4.87 (d and br. d, 2H, 6-CH₂, ²J 6.4 Hz), 7.2–7.4 (m, 5H, Ph). MS (EI, 70 eV), *m/z* (%): 261 (28) [M⁺], 230 (26), 201 (67), 171 (34), 142 (45), 128 (90), 115 (100), 105 (74), 91 (52), 77 (85), 42 (91), 41 (97). Found (%): C, 68.75; H, 7.32; N, 5.28. Calc. for C₁₅H₁₉NO₃ (%): C, 68.96; H, 7.28; N, 5.36.

8-(p-Tolyl)-5,7,11-trioxa-1-azatricyclo[7.3.1.0^{3,8}]tridecane **4**: yield 34%, mp 156–158 °C. ¹H NMR, d: 1.28 (narrow unresolved m, 1H, 3-H, $\Delta \nu_{1/2}$ 7.1 Hz), 2.4 (s, 3H, Me), 3.05–3.25 (m, 3H, 2-CH₂ and 13-H), 3.47 (br. d, 1H, 13-H, ²J 11.7 Hz), 3.53 and 3.66 (2d, 1H each, 4-CH₂, ²J 11.5 Hz), 3.78 (d, 1H, 10-H, ²J 11.6 Hz), 3.84–3.90 (m, 2H, 10-H and 9-H), 4.62 and 4.69 (2d, 1H each, 12-CH₂, ²J 10.3 Hz), 4.71 and 4.87 (2d, 1H each, 6-CH₂, ²J 6.4 Hz), 7.1–7.4 (AA'XX' system, 4H, Ar). MS, *mlz* (%): 275 (11) [M+], 244 (7), 215 (23), 198 (10), 142 (14), 128 (17), 119 (32), 99 (38), 91 (39), 71 (39), 42 (100), 41 (61). Found (%): C, 70.01; H, 7.58; N, 5.10. Calc. for C₁₆H₂₁NO₃ (%): C, 69.81; H, 7.64; N, 5.09.

4-Phenylpyridine 5: yield 32%, mp 76–78 °C. ¹H NMR and mass spectra are identical to those given in ref. 3.

4-(p-Tolyl)pyridine 6: yield 27%, mp 43–45 °C. ¹H NMR and mass spectra are identical to those given in ref. 5.

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