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Solid-phase synthesis of oxygen-bridged tetrahydropyridones

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Abstract—A solid-phase approach for the synthesis of oxygen-bridged tetrahydropyridones has been developed. A diamine is attached to Trt-Cl resin and condensed with different aliphatic or aromatic ketones and coumarin-3-carboxylic acid for 20 h and cleaved with 5% TFA in DCM, resulting in tri or tetracyclic products in moderate to high yield.

Although a large number of reactions have been studied for their use in combinatorial chemistry, relatively few are multi-component condensation reactions resulting in rigid cyclic structures.[1] Based on our continued interest in multi component reactions,[2] we decided to investigate a possible solid-phase approach for the synthesis of oxygen-bridged tetrahydropyridones (Fig. 1), which received initial attention due to its resemblance to morphine and the possibility to use them as intermediates in morphine synthesis.[3] The pharmacological relevance of oxygen-bridged tetrahydropyridones is based on the embedded activity of 1,4-dihydropyridines as calcium channel antagonists, with conformationally rigid sulfur-bridged dihydropyridines,[4] and the antidepressant lortalamine[5] as examples of pharmacologically active members of this class of compounds. Hitherto, the syntheses of oxygen-bridged tetrahydropyridones have been performed in solution mainly by three component reactions with coumarin carboxylic acid derivatives, ketones and primary amines. This route was first reported by Boehm[6] who refluxed coumarin-3-carboxylic acid and *p*-substituted anilines in acetone for 2 days. After subsequent workup concentrated HCl was applied for the decarboxylation step. Several groups have since used substituted 3-carboxyl,[7] 3-carbethoxy,[8,9] 3-acetyl[10–12] and 3-carboxamide[13] coumarins as starting materials. Reaction times differ from 3 to 10 days in room temperature, usually with a large excess of amine and ketone. An alternative route was presented by Svetlik et al.[14] who synthesized an oxygen-bridged tetrahydropyridone (Fig. 1, $R^1 = CH_3$, $R^2 = R^3 = R^4 = H$) via condensation of 4-(2-hydroxyphenyl) but-3-en-2-one with Meldrum's acid, although in low yield. A problem when this reaction is carried out, as reported, in homogenous solution, is that the isolation of the product from excess reagents is dependent on the very low solubility of the product. A more convenient route to these compounds would therefore have to have one component attached to a solid support and to use an excess of the other components to push the reaction to completion. The objective of the present work is therefore to evaluate if such a solid-phase approach is possible for this class of substances, which might be used in a combinatorial library synthesis.

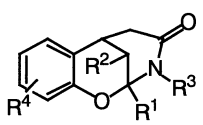

Figure 1. General structure of oxygen-bridged tetrahydropyridones.

1,3-Propylendiamine was attached onto a chlorotrityl polystyrene resin (Scheme 1) using a large molar excess of amine. The loading of amine was estimated to be 0.65 mmol/g.[15] The resin was subsequently incubated with 10–20 equiv. of a ketone and 5–10 equiv. of coumarin-3-carboxylic acid in NMP/THF 1/1 (v/v) containing molecular sieves 3 Å, at 40°C. After 20 h, the resin was thoroughly washed, dried and displayed a negative Kaiser test.[16] Cleavage from the resin was accomplished with 5% TFA in DCM with 1% triethylsilane as scavenger for 90 min. The TFA/DCM were evaporated and the crude material resuspended in aqueous NaOH and extracted into EtOAc.[17] If the ketone used was aliphatic, the product was soluble in water and could be extracted back into the aqueous phase with 1 M HCl (aq.) and lyophilized.

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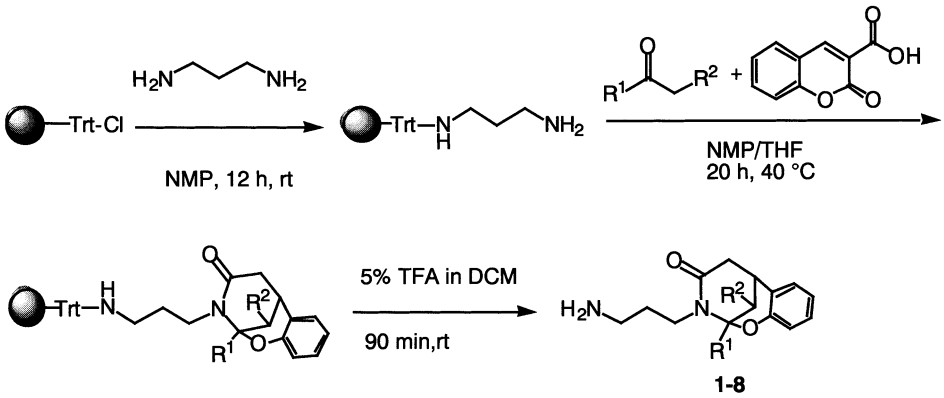
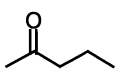
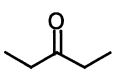
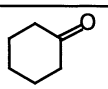
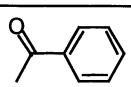
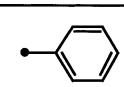
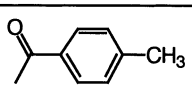
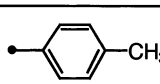
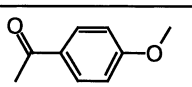
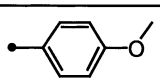
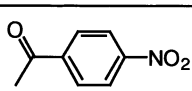
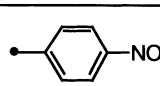


Scheme 1. Generalized scheme for the synthesis of oxygen-bridged tetrahydropyridones **1**–**8**.[17]

If the ketone was aromatic, the product could not be extracted into water. Instead, the combined organic phases were evaporated, dissolved in acetonitrile/water 1/1 (v/v) and lyophilized. HPLC/MS analysis of the crude material, at 254 and 215 nm, revealed medium to high purity of the correct product and yields were estimated both by absorbance and gravimetrically (Table 1). Representative HPLC profiles of substances **1**, **5** and **7** (Table 1) are shown in Fig. 2. An excess of the ketone and coumarin-3-carboxylic acid was important in order to obtain a good yield. When only 2.5 equiv. were used, the reaction did not go to completion within 20 h according to the Kaiser test and several side-products could be observed. If the reaction was performed for 24 h at room temperature using aliphatic ketones, oxygen-bridged tetrahydropyridones were formed as the major product. However, when aromatic ketones were used, the major product was more hydrophilic and 18 u heavier, indicating that the final step involves a loss of water. This suggestion is in accordance with the observation that yields were higher when 3 Å molecular sieves were used. For aliphatic ketones no significant increase in yield or purity was observed with prolonged reaction times up to 48 h, 40°C. In the case of aromatic ketones, a slightly higher purity, but not enough to motivate the long reaction time, was seen. NMR analysis was performed on compounds **1**, **6** and **8**[20] and are in accordance with previously published data[14] on this class of substances.

Table 1. R^1 and R^2 groups with corresponding ketone, purity and yield

Compound	Ketone	R^1	R^2	purity at 254/215 nm	Isolated Yield
1			H	78% / 78%	70%
2			H	65% / 85%	38%
3				65% / 85%	24%
4				63% / 54%	27%
5			H	65% / 85%	not isolated
6			H	69% / 74%	40%
7			H	31% / 84%	not isolated
8			H	65% / 67%	41%

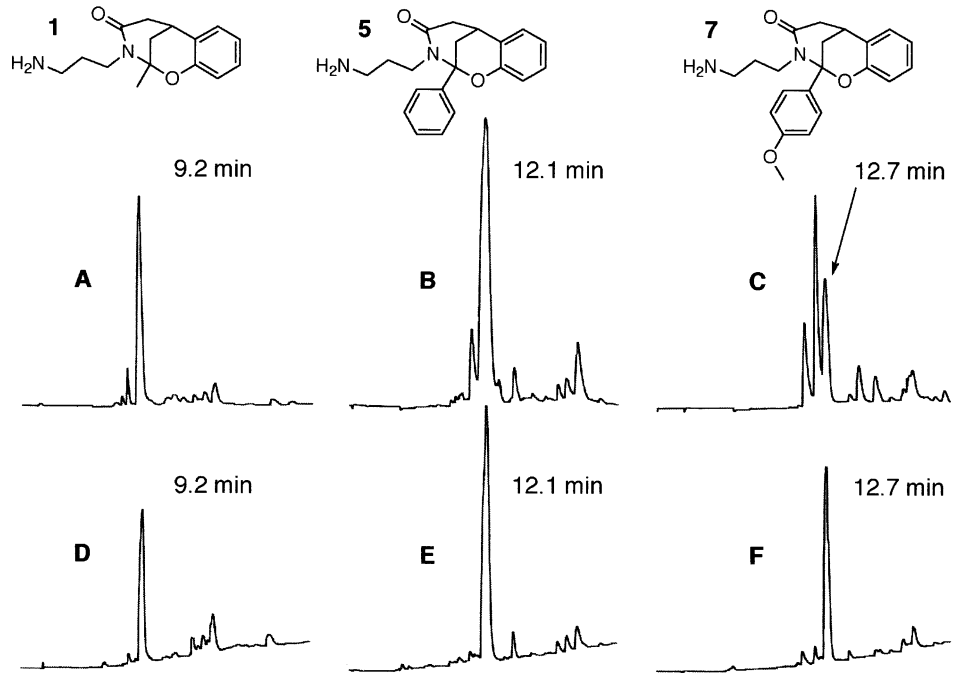


Figure 2. Analytical HPLC chromatograms[18] of **1**: **A** (254 nm), **D** (215 nm). **5**: **B** (254 nm), **E** (215 nm). **7**: **C** (254 nm), **F** (215 nm). Major peaks in **D**, **E** and **F** consists of correct $[M+H]^+$.[19]

We conclude that polycyclic oxygen-bridged tetrahydropyridones can be synthesized in moderate to high purity in a simple one-pot condensation reaction. This reaction might prove to be a valuable contribution to the collection of methods used in combinatorial chemistry, especially against the background that the majority of all potent drugs are relatively rigid polycyclic structures.

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15. As indicated by attaching Fmoc-Ala with standard peptide protocol, cleaving with 5% TFA in DCM with 1% triethylsilane as scavenger and UV analysis at 300 nm with Fmoc-Ala as reference.
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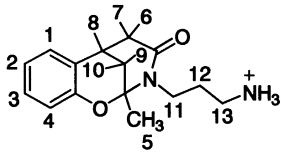
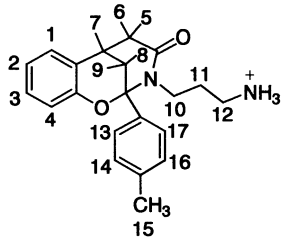
17. Typical procedure for the synthesis of oxygen-bridged tetrahydropyridones. Synthesis of compound **1**: chlorotrityl resin (100 mg) was suspended in dry NMP (3.5 ml) and agitated at room temperature with an excess of 1,3-diamino propane (150 μl, 1.8 mmol). The resin was filtered, washed (EtOH, 2×DMF, 2×(5% DIPEA/DCM, DMF), 3×DCM) and dried. The substitution was estimated to be 0.65 mmol/g.[15] The amino substituted resin was resuspended in dry NMP/dry THF, 1/1, 3.2 ml and incubated with acetone (51 μl, 0.7 mmol, 10 equiv.),

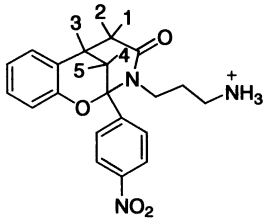
coumarin-3-carboxylic acid (66.5 mg, 0.35 mmol, 5 equiv.) and 3 Å mol. sieves at 40°C for 20 h. After thorough washing (3×NMP, 2×EtOH, 2×DMF, 2× (5% DIPEA/DCM, DMF), 3×DCM), the resin was dried and produced a negative Kaiser test.[16] Cleavage from the resin was accomplished with 5% TFA in DCM with 1% triethylsilane as scavenger. After 90 min at room temperature the resin was filtered and washed with 5% TFA in DCM. The TFA/DCM mixtures were pooled, evaporated, dissolved in aqueous NaOH and extracted with 3×EtOAc. The organic phase was evaporated to 1/3 and extracted into the aqueous phase with 3×1 M HCl (aq.) and lyophilized. The crude product obtained was analyzed (Fig. 2, **A** and **D**) and purified on RP-HPLC[18] (8.6 mg, 70%, based on initial loading of amino substituted resin).

18. HPLC analyses were performed on a Machery–Nagel KS 100/4 Nucleosil® 120-3 C_{18}, elution gradient was 20–80% of B in 18 min. HPLC purifications were performed on a Machery–Nagel SP 250/10 Nucleosil® 120-7 C_{18}, elution gradient was 20–80% of B in 29 min. Solvent A was 0.1% TFA/H_2O and solvent B was 0.1% TFA/acetonitrile.
19. Molecular weight determinations were made on an Applied Biosystems BIO-ION 20 plasma desorption mass spectrometer, using ^{252}Cf isotope as a source of fission fragments.
20. ^1H NMR data: **1** (400 MHz, $CDCl_3$): δ 8.13 (m, 3H, NH_3^+); 7.17–7.13 (dt, 1H, $J=1.6$, 7.9 Hz, H-3); 7.11 and 7.09 (2d, 1H, $J=1.4$, 7.7 Hz, H-1); 6.97–6.92 (dt, 1H, $J=1.0$, 7.6 Hz, H-2); 6.77 and 6.75 (2d, 1H, $J=0.9$, 8.2 Hz, H-4); 3.70 (m, 2H, H-13); 2.58 (br, 2H, H-11); 2.10 (br, 2H, H-12); 3.14 (m, 1H, H-8); 2.81 and 2.77 (2d, 1H, $J_{7,9}=4.4$ Hz, $J_{6,7}=17.6$ Hz, H-7); 2.64 (d, 1H, $J_{6,7}=18.0$ Hz, H-6); 2.29 and 2.26 (2d, 1H, $J_{8,10}=2.1$ Hz, $J_{9,10}=13.5$ Hz, H-10); 2.24 and 2.21 (2q, 1H, $J_{8,9}=2,3$ Hz, $J_{7,9}=4.0$ Hz, $J_{9,10}=13.4$ Hz, H-9); 1.78 (s, 3H, H-5).





6 (400 MHz, $CDCl_3$): δ 7.88 (m, 3H, NH_3^+); 7.27 (br, 2H, H-13, H-17); 7.25 (br, 2H, H-14, H-16); 7.24–7.19 (dt, 1H, $J=1.6$, 7.7 Hz, H-3); 7.16 and 7.14 (2d, 1H, $J=1.5$, 7.7 Hz, H-1); 7.02–6.98 (dt, 1H, $J=1.0$, 7.4 Hz, H-2); 6.95 and 6.94 (2d, 1H, $J=0.9$, 8.1 Hz, H-4); 3.51 (m, 2H, H-12); 3.22 (m, 1H, H-7); 2.94 and 2.90 (2d, 1H, $J_{6,8}=4.6$ Hz, $J_{5,6}=17.6$ Hz, H-6); 2.78 and 2.74 (br t, 1H, $J_{5,7}=2.2$Hz, $J_{5,6}=17.6$ Hz, H-5); 2.60 (br, 2H, H-10); 2.18 (br, 2H, H-11); 2.55 and 2.51 (2d, 1H, $J_{7,9}=1.8$ Hz, $J_{8,9}=13.9$ Hz, H-9); 2.40 (s, 3H, H-15); 2.30 and 2.26 (2q, 1H, $J_{7,8}=2,7$ Hz, $J_{6,8}=4.4$ Hz, $J_{8,9}=13.9$ Hz, H-8).



8 (400 MHz, DMSO-d_6): δ 8.36 and 8.34 (2d, 2H, $J=1.1$, 7.6 Hz, Ph); 7.98 (br, 3H, NH_3^+); 7.72 (d, 2H, $J=1.1$ Hz, Ph); 7.28-7.22 (dt, 1H, $J=1.6$, 7.6 Hz, Ph); 7.24 and 7.22 (2d, 1H, $J=1.4$, 7.9 Hz, Ph); 7.06–7.01 (dt, 2H, $J=1.1$, 7.4 Hz, Ph); 3.46 (m, 2H, -CH_2-CH_2-NH_3^+); 3.29 (m, 1H, $J_{1,3}=2.2$ Hz, H-3); 3.06 and 3.02 (2d, 1H, $J_{2,3}=4.8$ Hz, $J_{1,2}=17.2$ Hz, H-2); 2.84 (m, 2H, N-CH_2-CH_2-); 2.76 and 2.71 (2t, 1H, $J_{1,3}=2.2$ Hz, $J_{1,2}=17.2$ Hz, H-1); 2.64 and 2.61 (2d, 1H, $J_{3,5}=1.8$ Hz, $J_{4,5}=13.5$ Hz, H-5); 2.42 (m, 2H, -CH_2-CH_2-CH_2-); 2.30 and 2.27 (2q, 1H, $J_{3,4}=2.9$ Hz, $J_{2,4}=4.3$ Hz, $J_{4,5}=13.5$ Hz, H-4).