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Solid phase synthesis of praziquantel

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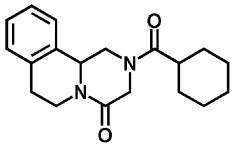
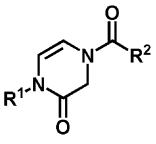
Abstract—The first solid phase synthesis of the important anthelmintic praziquantel is described. The synthesis is rapid and efficient. The method may be extended to the synthesis of libraries of urgently needed replacements for this drug.

Praziquantel (PZQ, **1**) is the drug of choice for the treatment of schistosomiasis (Bilharzia), a debilitating parasitic infection that currently affects around 200 million people worldwide and one of the most burdensome of the neglected diseases.[1] PZQ qualifies for the title 'wonderdrug' in that it is inexpensive to synthesise, is safe at high doses and is very effective. Off-patent, it is now being distributed to select African countries in mass chemotherapy programmes.[2] Inevitably this will increase the likelihood of the emergence of resistance or tolerance,[3a,b] a process that has been modelled in the laboratory after several generations of a simple artificial selection process.[3c] This is a dangerous situation because there exist no back-up drugs for the treatment of schistosomiasis.



PZQ, 1



Generic Enediamide, 2

Several syntheses of PZQ have been reported,[4] including our own modular strategy developed to use mild reagents, which we envisaged would be useful for the construction of libraries of PZQ analogues.[5] Our synthesis involved an aryl radical closure onto the reactive double bond of an enediamide nucleus (or acyl-tetrahydropyrazinone, **2**), a ring system in which we have a current interest.[6] This same motif was also observed in previous syntheses of PZQ, but is otherwise virtually absent from the chemical literature.

We report here the first solid phase synthesis of praziquantel. The synthetic scheme (Scheme 1) modifies existing peptide acetal/cyclisation methodology, and uses a traceless linker approach where the resin is attached to the growing precursor via an acetal.[7] The intention was to build the precursor in such a way that acidic cyclisation would also liberate PZQ from the solid support. The linear acetal leaves the support as an acyliminium ion, which undergoes a Pictet–Spengler bond formation to generate PZQ. We wished to generate PZQ without contamination by the enediamide **8**, the stable conjugate base of the reactive acyliminium intermediate.

Our approach met with failure when we employed commercial resins based on polyethylene glycol (PEG)-grafted polystyrene because the acidic cyclisation conditions we employed appeared to cleave PEG-based by-products from the support, complicating the final purification. We hence synthesised solid-supported bromoacetal **4** from hydroxymethyl polystyrene (**3**).[7] The synthesis proceeded in higher yield with the inclusion of a heterogeneous drying agent in the reaction mixture. The bromine level of resin **4** was close to that calculated from the loading of the starting material.[8] Subsequent displacement of the bromine with phenylethylamine in DMSO[7] as solvent gave superior yields to the use of DCM as judged by the elemental analysis of the products (Table 1). This was surprising because DCM gives far better swelling of the resin, judged

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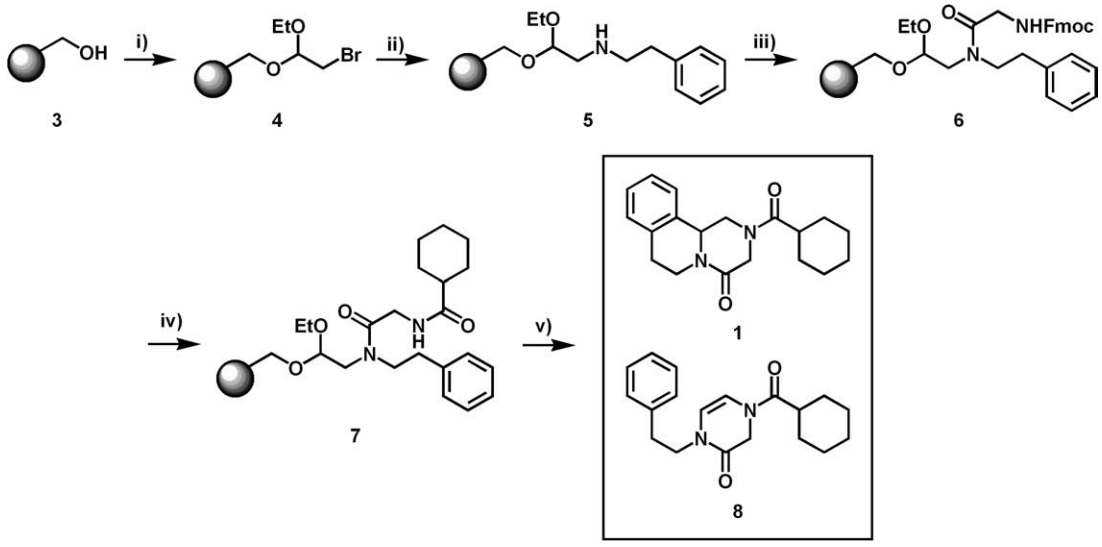


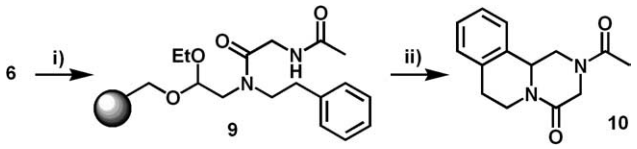
Scheme 1. Initial solid phase synthetic scheme. Reagents and conditions: (i) anhydrous quinoline *p*-toluenesulfonate then bromoacetaldehyde diethylacetal; (ii) 2-phenylethylamine in DMSO; (iii) Fmoc-glycine-OH, PyBroP, HOBr, DIPEA; (iv) 20% piperidine in DMF then cyclohexanecarboxylic acid, PyBroP, HOBt, DIPEA; (v) $MeSO_3H$ in $MeNO_2$ or TFA in DCM.

Table 1. Bromine analysis for selected resins

Resin	Solvent used in resin preparation	%Br	
		Calculated	Found
4	—	6.8	5.9
5	DMSO	0	1.7
5	DCM	0	6.9

visually. The level of residual bromine could not be reduced with further couplings.

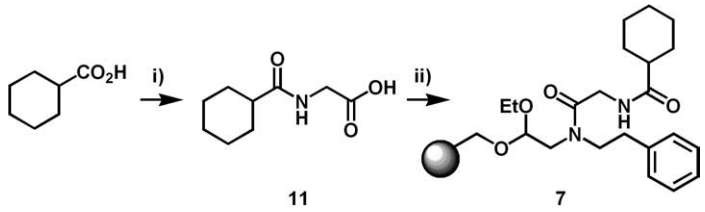
The sequence of reactions leading to **7** proceeded unremarkably, with the expected mass changes in the resins and carbonyl stretching frequency changes in the IR spectra of the resins.[9] Several cyclisation conditions were attempted for the conversion of **7** into PZQ including methanesulfonic acid in nitromethane and trifluoracetic acid in dichloromethane, conditions that had been explored during our previous investigations.[5] We were unable to discover conditions, which provided us with any isolable product. We inserted a capping step (acetyl chloride in pyridine) prior to reaction with phenylethylamine in case residual hydroxyl groups on the resin were interfering in the cyclisation, but again were disappointed not to isolate any material after the cyclisation. A milder cyclisation with tin triflate in DCM liberated a compound from the resin, which we did not characterise because the ^1H NMR spectrum, while containing peaks indicating the formation of an enediamide nucleus, clearly did not contain any signals for the cyclohexyl moiety. The difficulties we were encountering were either due to loss of the cyclohexyl group upon cyclisation or due to a poor yield in the coupling of the cyclohexanecarboxylic acid to the resin. We next subjected resin **6** (following deprotection) to reaction with acetyl chloride in pyridine, followed by acid-catalysed cyclisation using 20% methanesulfonic acid in nitromethane (Scheme 2). This furnished the PZQ analogue **10**, quantitatively, after simple filtration through a short plug of silica.



Scheme 2. Successful cleavage of the acyl-PZQ analogue from the resin. Reagents and conditions: (i) 20% piperidine in DMF then acetyl chloride in pyridine; (ii) 20% $MeSO_3H$ in $MeNO_2$, 60 °C, 16 h.

Encouraged by this result, we sought alternatives to the coupling of the cyclohexyl moiety in our original scheme. We noted in previous reports of PZQ synthesis that introduction of the cyclohexyl moiety after cyclisation[4f] gave better yields than when the cyclohexyl was present initially,[4g] and the introduction of the cyclohexyl group was also the last step in other syntheses.[4b,d] In our hands, cyclisation of resin **6** (after removal of the Fmoc group) using 20% methanesulfonic acid in nitromethane for 16 h at 60 °C, followed by reaction of the crude filtrate with cyclohexylchloride (DCM, Na_2CO_3, 60 °C, 16 h) did not generate any desirable or easily identifiable products.

We therefore performed the apparently troublesome glycine-cyclohexyl coupling off-resin. Amide **11** was synthesised from cyclohexanecarboxylic acid and glycine benzyl ester (Scheme 3).[5] Coupling of **11** to deprotected resin **6** generated **7**, which, when cyclised with 20% methanesulfonic acid in nitromethane at 60 °C for 16 h and the filtrate purified by passage through a short plug of silica, successfully gave PZQ (**1**) in a moderate yield of 57% (for the entire sequence, based on the loading of resin **3**).

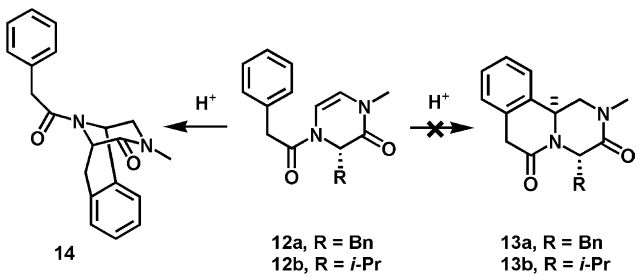


Scheme 3. Alternative route to the cyclisation precursor. Reagents and conditions: (i) glycine benzyl ester *p*-toluenesulfonate, HOBt, EDC, DMAP, 16 h, then 10% Pd/C, H_2, 90 min; (ii) **6** after 20% piperidine/DMF wash, PyBroP, HOBt, DIPEA.

The final cyclisation also indicates that the problem with the synthetic route as originally planned was not necessarily due to the presence, per se, of the cyclohexyl group, but arises from a difficult coupling between cyclohexanecarboxylic acid and the resin-bound amine (deprotected **6**). Why this should be problematic when coupling with acetyl chloride proceeded smoothly, or when coupling between cyclohexanecarboxylic acid and glycine benzyl ester in solution was unremarkable is unclear.

A comparison with our previous studies on the acidic cyclisation of heterocycles is noteworthy. In the case of the related ring system **12**, we found that strongly acidic conditions were unsuitable for a final Pictet–Spengler step (to give **13**) because the rigidity of the exocyclic amide prevents the requisite orbital overlap for this reaction (Scheme 4).[5] In fact we observed preferential cyclisation of a competing aromatic ring present on our heterocycle **12a** (to give **14**), which prompted our alternative radical-based approach. The constraints on this reactivity were severe, in that the desired sequence did not proceed even when the valinyl analogue **12b** was employed, where cyclisation to the bridged ring system of **14** is not possible. Such constraints do not apply to the chemistry described for the synthesis of PZQ since the relevant aromatic ring is not attached to the exocyclic amide (in other words, the direction of the amide bonds is 'the other way round'), allowing much greater flexibility in the cyclisation step. Strongly acidic cyclisations are acceptable in the synthesis of PZQ: the question of whether these conditions are suitable for the synthesis of PZQ analogues with competing or reactive functional groups present will be addressed in a future article.

We have described the first solid phase synthesis of PZQ. The synthesis consists of five steps and is rapid (less than 36 h reaction time for the longest linear sequence), easily adaptable to a library format and generates PZQ in an overall yield of 57%.



Scheme 4. Competing cyclisations in enediamide chemistry where the amide bond direction is reversed.

Acknowledgements

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Supplementary data

Experimental descriptions and spectroscopic data for all compounds. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.12.073.

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8. Calculations of yields and expected values for elemental analyses are performed as follows. For a starting material resin of loading x_0 (mmol g^{-1}), the hypothetical monomer (i.e., the hypothetical chain that contains one functional group) has mass $M = 1000/x_0$. If a reaction is carried out that involves a change in mass of this monomer of m, the new loading of the product resin is given by $1000/[(1000/x_0)+m]$. The loading and the value of M may be used to calculate expected combustion analyses. For example, for bromoacetal resin **3**, the starting material had a loading of 0.98 mmol g^{-1}, giving $M = 1020$. The reaction to give **3** has $m = 151$ (the product hypothetical monomer has mass 1171) giving a product loading of 0.85 mmol g^{-1}, an expected product mass of 5.7 g from 5.0 g starting material and an expected bromine content of 6.8% for the product. Yield calculations for cumulative non-quantitative reactions are complex.
9. Typically IR spectra were recorded by the swelling of a small quantity of beads on a NaCl plate with DCM followed by squashing of the resin under another NaCl plate, and acquiring while the resin is still wet.
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