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Thiol-mediated free radical cyclisations of isocyanides on solid support

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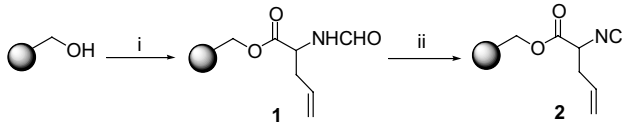
Abstract—Three novel polymer-supported isocyanides have been synthesised, from commercial Wang and HMBA-AM resins, and reacted under radical conditions with 2-mercaptoethanol and ethanethiol to give the corresponding pyrrolidine or pyroglutamic acid derivatives in good yields.

Radical reactions of isonitriles date back to the 1960s when Saegusa et al.[1] discovered the isonitrile–nitrile isomerisation mediated by methyl or stannyl radicals, but only since 1991 have radical reactions with isonitriles been successfully employed in the synthesis of heterocyclic compounds.[2] In the last decade the emergence of combinatorial chemistry has stimulated intensive efforts in the application of reactions, broadly used in solution, to solid phase synthesis but examples of radical reactions are still relatively limited.[3]

The extension of isonitrile radical chemistry to solid phase reactions could allow further progress in combinatorial organic synthesis, with the added advantage that handling of often noxious isocyanides in solution could be avoided. We now report the synthesis of three novel polymer-supported alkenyl isocyanides and their use in thiol-mediated radical cyclisations.

Our first objective was to find a simple route to the resin bound alkenyl isocyanide **2**. Formylamino resin **1** was synthesised from Wang resin and 2-formylaminopent-4-enoic acid,[4] using DIC/DMAP coupling conditions (Scheme 1). The reaction was checked by IR spectroscopy, which showed the appearance of the expected carbonyl signal, and by MAS ^{1}H NMR, which also gave a spectrum consistent with the expected product.[5]



Scheme 1. Synthesis of polymer-supported isocyanide **2**. Reagents and conditions: (i) 2-formylamino-4-pentenoic acid, DIC/DMAP in CH_2Cl_2, 5 h at rt; (ii) $POCl_3$, Et_3N in CH_2Cl_2, 3 h at 0 °C.

The next step was the dehydration of **1** to give the corresponding alkenyl isocyanide **2**, which was best achieved with a large excess of $POCl_3/Et_3N$, under rigorously dry conditions. IR spectroscopy showed the expected isocyanide absorption at 2150 cm^{-1} and MAS ^{1}H NMR showed the disappearance of the formyl proton,[5] indicating completion of the reaction. Resin **2** was then cyclised with 2-mercaptoethanol and ethanethiol[2a,j] to give resins **3** and **4**, respectively (Scheme 2).

The reactions were monitored by IR spectroscopy and completion was indicated by disappearance of the isocyanide absorption at 2150 cm^{-1}. A large excess of thiol and radical initiator were employed in order to obtain optimum results, whilst shorter reaction times gave lower yields.

Cleavage of **3** with 95% TFA gave the expected pyroglutamic acid derivative **5** as a mixture of diastereoisomers (1:1 by ^{1}H NMR), in 66% yield after column chromatography.[6] Cleavage of resin **4** under standard TFA conditions resulted in hydrolysis of the product to **5**, but

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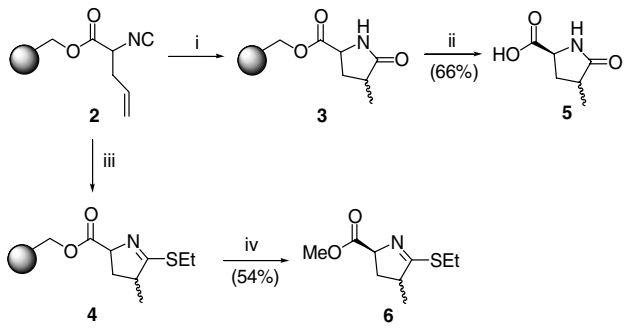
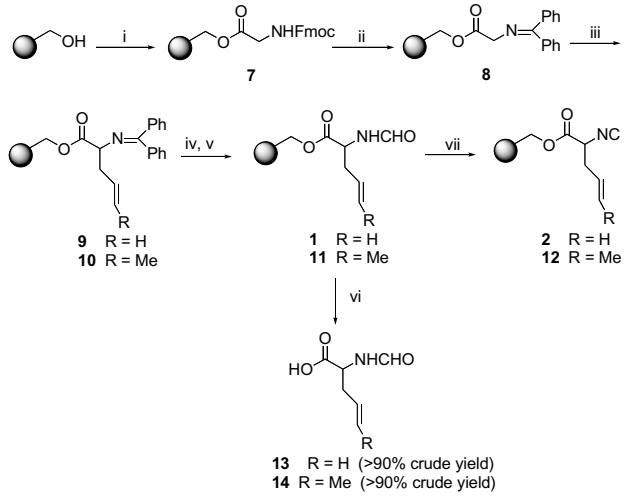


Scheme 2. Radical cyclisation of polymer-supported isocyanide **2** with ethanethiol and 2-mercaptoethanol. Reagents and conditions: (i) 2-mercaptoethanol (35 equiv), AIBN (5 equiv), DMF, 48 h at 50 °C; (ii) 95% TFA in CH_2Cl_2, 5 h at rt; (iii) ethanethiol (35 equiv), AIBN (5 equiv), DMF, 48 h at 80 °C; (iv) MeOH/Et_3N/KCN, 24 h at reflux.

nucleophilic cleavage conditions were used successfully to give the expected pyrroline **6** in 54% yield (as a 1:1 diastereomeric mixture).[6]

These preliminary results prompted us to investigate the general applicability of this methodology to the synthesis of pyroglutamates. To develop a general synthetic route to isocyanide resins with variation of the alkenyl side chain, we used the O'Donnell 'Solid Phase UPS' methodology (Scheme 3).[7]

Fmoc-glycine resin **7** was prepared by coupling the protected amino acid to commercial Wang type resin,[8] using standard coupling conditions. The reaction was repeated twice to ensure complete coupling. The Fmoc protecting group was removed with piperidine, and the free amino group was reacted with benzophenone imine[9] to activate the resin bound glycine for the next alkylation step. Deprotonation and alkylation of the benzophenone imine resin **8** with allyl bromide or crotyl bromide was accomplished using the organic-soluble, neutral, strong iminophosphorane 'Schweisinger base', BEMP.[10] The imine residue of the alkylated resins **9** and **10** was then hydrolysed, neutralised to afford the free amino group, and finally formylated, with acetic formic anhydride,[4] to obtain the desired formylamino resins **1** and **11**. All the reactions were monitored by IR spectroscopy and colorimetric tests where possible. Small amounts of resins **1** and **11** were then treated with trifluoroacetic acid to cleave the product from the solid support. The expected alkenyl formylamino acids **13** and **14** were obtained in excellent crude yields and good purity (>90% by ^1H NMR). Subsequent dehydration of resins **1** and **11** afforded the desired polymer-supported isocyanides **2** and **12**. The isocyanides were treated with 2-mercaptoethanol, and the cyclised products cleaved from the solid support using TFA (Scheme 4).

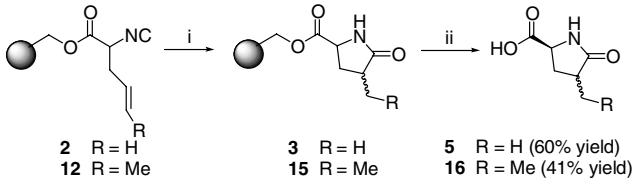


Scheme 3. Solid phase synthesis of polymer-supported isocyanides from glycine. Reagents and conditions: (i) Fmoc-GlyOH, DIC/DMAP, DCM, 3 h rt; (ii) (a) 20% piperidine in DMF; (b) $Ph_2C{=}NH$, AcOH, NMP, 12 h at rt; (iii) R–X, BEMP, NMP, 12 h at rt; (iv) (a) $NH_2OH{\cdot}HCl$, THF, 5 h at rt, (b) 20% DIPEA, NMP; (v) $(CH_3CO)OCHO$, NMP, 3 h at rt; (vi) 50% TFA in CH_2Cl_2, 3 h at rt; (vii) $POCl_3$, Et_3N in CH_2Cl_2, 3 h at 0 °C.

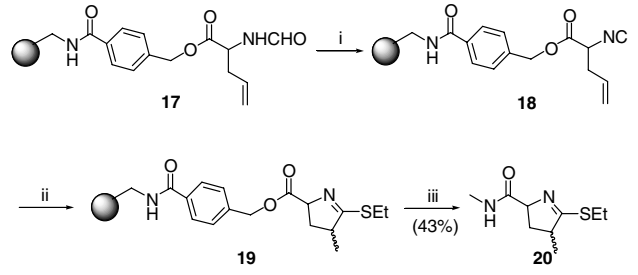
After cleavage and purification by chromatography, the expected compounds **5** and **16**[6] were obtained in 60% and 41% isolated yields, respectively, again as 1:1 mixtures of diastereoisomers.

In order to extend this methodology further we also synthesised an alkenyl isocyanide on HMBA-AM resin,[11] which can be readily cleaved under nucleophilic conditions (primary/secondary amines) giving access to amide derivatives, for example, **20** (Scheme 5).

Resin **17** was synthesised from HMBA-AM resin and 2-formylamino-4-pentenoic acid and dehydrated to give isonitrile **18** and then cyclised with ethanethiol under



Scheme 4. 2-Mercaptoethanol mediated radical cyclisation of isocyanides **2** and **12**. Reagents and conditions: (i) 2-mercaptoethanol (35 equiv), AIBN (5 equiv), DMF, 48 h at 50 °C; (ii) 50% TFA in CH_2Cl_2.



Scheme 5. Synthesis and cyclisation of an alkenyl isocyanide immobilised on HMBA-AM resin. Reagents and conditions: (i) $POCl_3$, Et_3N in CH_2Cl_2, 3 h at 0 °C; (ii) ethanethiol (35 equiv), AIBN (5 equiv), DMF, 48 h at 80 °C; (iii) $MeNH_2$ in THF, 2 h at rt.

standard conditions. Cleavage of pyrroline resin **19** with methylamine afforded **20** in 43% overall yield, as a 1:1 mixture of diastereoisomers.[6]

In conclusion we have demonstrated the extension of isocyanide radical chemistry to solid phase synthesis, by synthesising three novel polymer-supported isocyanides (**2**, **12** and **18**) which give access to pyroglutamates and 2-mercaptopyrrolines by free radical cyclisations mediated by thiols, in good overall yields.

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6. All new compounds were characterised by ^{1}H and ^{13}C NMR, IR and HRMS.
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