A simple amide protecting group: synthesis of oligoamides of Nylon 6

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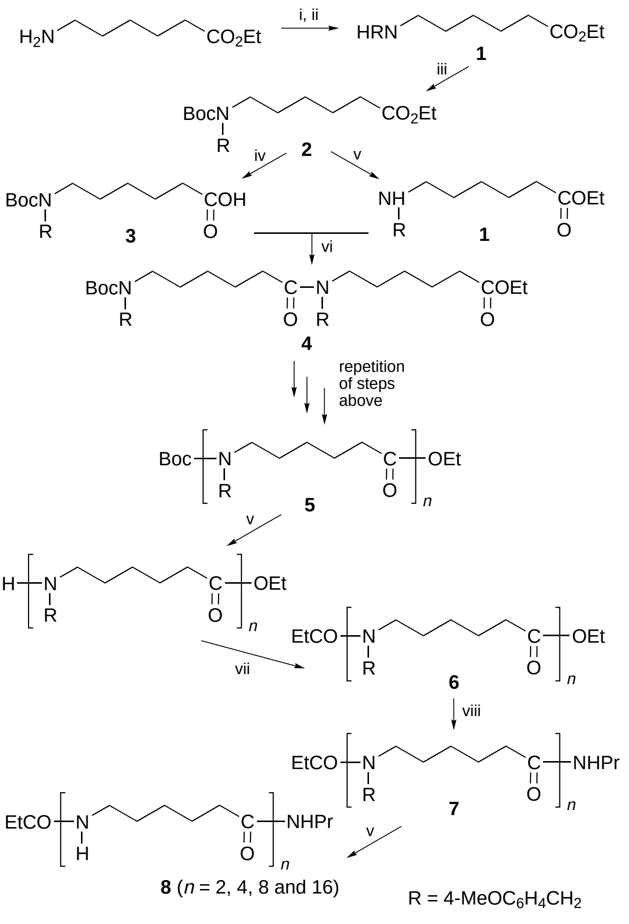
The 4-methoxybenzyl group (R) in amide groups NR(C=O) renders all intermediates in the synthesis of oligomers of Nylon 6 soluble in common solvents and is readily removed in boiling trifluoroacetic acid.

Wallace Carothers described the first use of a disecondary diamine to introduce 'rubberiness' into a polyamide in an early patent—the preparation of poly(N,N'-dimethylpentamethylenesuccinamide), $\{N(Me)(CH_2)_5N(Me)(C{=}O)(CH_2)_2)(C{=}O)]_n\}$;[1] the hydrogen-bonding properties due to the NH(C=O) group, which confer many of the desirable properties of Nylons, were lost from the point of view of normal use at that time, textiles. Soon afterwards, other workers investigated the use of *N,N'*-dialkyl derivatives of 1,6-hexamethylenediamine (alkyl = methyl, ethyl, isobutyl and benzyl) for incorporation into alkyl Nylon 6,10 polymer,[2] but very little has been published since in this area. The most noticeable physical property affected in these polymers compared with the non-alkylated materials was a marked increase in solubility in common organic solvents.



Scheme 1 *Reagents and conditions*: i, 4-$MeOC_6H_4CHO$; ii, $NaBH_4$; iii, Boc_2O; iv, NaOH, the H^+; v, TFA, 25 °C; vi, DCC, 1-hydroxybenzotriazole; vii, EtCOCl; viii, $PrNH_2$, KCN(cat.); ix, TFA, reflux

The best science is carried out on pure compounds. Recently, the preparation of some monodisperse linear long-chain alkanes was described,[3] materials of interest for relating their properties as models to those of commercial polythene, a polydisperse substance; the folding of the molecular chains in these compounds is of particular interest.[4] The study of pure oligoamides of the Nylon family is expected to provide even more insights into the nature of the chain-folding process since both amide and alkyl folds are possible.

We have exploited the lack of inter-chain hydrogen-bonding in *N*-alkylated amides to make soluble intermediates which were purified by chromatography on silica to produce pure 'end-capped' Nylon 6 oligomers. These compounds have been made previously,[5] but their purity could not be monitored. While relatively little work has been carried out on amide protecting groups,[6] we have now discovered that the 4-methoxybenzyl group in an amide $[N(CH_2C_6H_4OMe\text{-}4)(C{=}O)]$ is an excellent protecting group, conferring solubility in common solvents† on all derivatives, and being readily removed by boiling TFA. Scheme 1 shows the initial formation of the partially protected ethyl ester of acid **1** and its final protection to give the *N*-Boc derivative **2**, the starting material for an iterative synthesis. The first protected amide linkage in **4** was formed from **3** and **1** by a method used in peptide chemistry.[7] The Boc group in **4** was removed by TFA at room temperature and the chain-doubling reaction repeated successively to give first the fully protected dimer **5** (n = 2), then the tetramer **5** (n = 4) *etc.* up to the hexadecamer **5** (n = 16). Individual 'end-capped' amides were obtained by deprotection of the *N*-terminus in **5**, followed by propanoylation to give **6**, and conversion of the ethoxycarbonyl terminus to the propylamide derivative **7**.‡ Finally, removal of the amide protecting group gave 'end-capped' oligomers **8** (n = 2, 4, 8 and 16) of Nylon 6.§ The purity of the intermediates, formed in high yielding reactions, could be monitored by HPLC and their structures confirmed by ^1H NMR spectroscopy. The final end-capped Nylon 6 oligomers **8** were found to be soluble in CD_3CO_2D at 80 °C, which enabled the complete confirmation of their structures to be carried out by ^1H NMR spectroscopy at 500 MHz. Currently, we are employing similar methodology for the synthesis of oligomers of Nylon 6,6 and Nylon 4,6.

The 4-methoxybenzyl group as a protecting group on nitrogen in an amide not only renders the parent molecule more soluble (the property exploited in this work); it also removes a potentially acidic hydrogen which could be incompatible in further types of reaction. It would then assume the role of a classical protecting group, and could be introduced into a NH(C=O) bond *via* treatment with LDA–4-methoxybenzyl bromide.

Footnotes and References

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† Binary mixtures of appropriate solvents for chromatography were selected from the following: CH_2Cl_2, MeOH, EtOAc, Et_2O and light petroleum (bp 40–60 °C).

‡ All the intermediates **2**–**7** in Scheme 1 were viscous liquids/gums; compound **1** was a liquid, bp 148–151 °C/0.01 mm Hg.

§ An unidentified solid precipitated during the final deprotection of the amide groups in **7**. The TFA was removed *in vacuo* and the residue was found to dissolve completely in CH_2Cl_2, the oligoamide being rendered soluble by traces of trifluoroacetic acid. Treatment of the solution with dilute sodium hydrogen carbonate solution brought about the immediate precipitation of **8** in each case.

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