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The Selective *O*-Acylation of Hydroxyproline as a Convenient Method for the Large-Scale Preparation of Novel Proline Polymers and Amphiphiles

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In this work we show how a direct *O*-acylation of *trans*-4-hydroxy-L-proline with acyl chlorides in trifluoroacetic acid makes a range of novel proline derivatives readily available on large-scale. No protecting groups or chromatographic techniques are involved in any of the procedures, and certain amphiphilic proline derivatives, which recently have received interest in synthesis, are now potentially some of the most readily accessible organocatalysts. The selective acylation was also utilized in the synthesis of a novel high-load proline polymer, poly(*O*-acryloyl-*trans*-4-hydroxy-L-proline), a polymer with the highest proline loading reported and for which classical methods failed for its preparation.

Introduction

After nearly a decade of intense research within organocatalysis, the simple amino acid proline is still the most versatile and useful of the organocatalysts.[1] Not only has it the ability to catalyze an especially broad range of useful synthetic transformations, but being a naturally abundant amino acid, its availability both in terms of economic cost and practical simplicity gives it a usefulness that other organocatalysts have not yet managed to rival. However, unmodified proline suffers some notable and well-known disadvantages. Its marked polarity makes it insoluble in most non-aqueous solvents, a notable disadvantage because good enantiomeric induction can be difficult or impossible to obtain in aqueous media.[2] Recently, a range of novel amphiphilic proline derivatives have caught the attention of the synthetic community and proven extremely efficient in asymmetric aldol reactions in the presence of water.[3] Although superficially very simplistic, their widespread and large-scale use as a lipophilic or amphiphilic proline is hampered by their cumbersome preparation. To attach the necessary hydrophobic moieties, both the acid and the amino functionality of hydroxyproline have to be protected/deprotected (Scheme 5) and the intermediates purified by chromatography. In fact, considering the extensive interest that organocatalysis has received and the importance of proline in particular, it is surprising that so few genuinely effective procedures for the preparation of simple (hydroxy)-proline derivatives have been reported. We have developed a direct and selective *O*-acylation of hydroxyproline in CF_3CO_2H or a more powerful CF_3CO_2H/CF_3SO_3H system that gives crystalline hydrochlorides of *O*-acyl derivatives of hydroxyproline in one step without the need of any protecting groups. The free amino acid is then obtained as crystals of good purity by precipitation from a solution of the hydrochloride salt in lower alcohols with propylene oxide.

Catalyst immobilization is a renowned method to facilitate product isolation and catalyst recovery. Since the "rebirth" of organocatalysis in 2000, several procedures have been disclosed in the literature for the support anchoring of proline or close derivatives.[4–7] The majority of them use the readily available and optically pure proline derivative *trans*-4-hydroxy-L-proline (**1**) as starting material, a constituent of the protein collagen that is produced in industrial quantities at low cost.[8] The secondary alcohol of this proline derivative serves as a convenient point of attachment to a solid support, located some distance away from the amino acid functionalities essential for the organocatalytic activities,[4–6] although linkage through the acid functionality of proline is also possible for some reactions.[7] Proline, a close derivative or a proline-terminated peptide have been immobilized by molecular spacers onto the microporous Merrifield resin (crosslinked polystyrene),[4] polyethylene glycol (PEG),[5a–5d] linear polystyrene,[5e–5f] mesoporous silica,[6] polystyrene-PEG resins,[4h,7c–7e] macroporous polystyrene,[4h] polystyrene resins containing specialized linkers[7b] or crossbinders[9] and acrylamide-based resins.[7d] Importantly, several of them have much higher stereoselectivity than the unsupported catalysts, the supported system creating a primitive type of artificial aldolase.[4h]

Although the immobilization of proline has been undertaken on quite an extensive assortment of prefabricated solid supports since 2001, any dedicated macromolecular synthesis where side-chain-anchored hydroxyproline-bearing monomers are (co)polymerized seems to be entirely absent.

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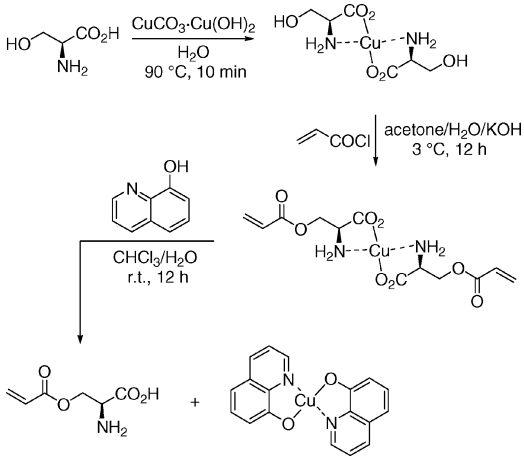
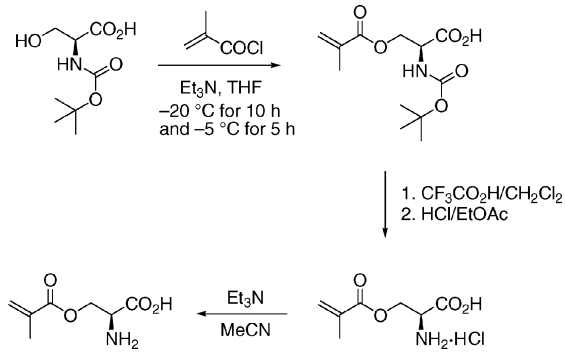
The side-chain (meth)acrylic derivatives of α-amino acids is an interesting class of chiral monomers with great potential for the preparation of biocompatible polymers for use in implants, medical devices, additives for food and cosmetics, optical lenses and fibers for plastics.[10] Some of them are also powerful and useful selective metal scavengers.[11] Although the more benign and easily prepared *N*-acryloyl and *N*-methacryloyl amides of amino acids and their polymers have been known since at least the early 1960s,[12] the literature on the side-chain (meth)acrylic analogues is surprisingly scarce.[11,13–17] We believe this could be connected to the fact that the procedures reported in the literature until now, all within the polymer community, give the side-chain (meth)acrylic amino acids in free unblocked form (i.e. not as a salt), a product destined to be extremely susceptible to conjugate addition. Interestingly, the preferred method for their preparation has its roots all the way back to amino acid chemistry from the early 1940s.[18] The amino acid functionalities are masked by coordination with copper ions, whereas the side-chain hydroxy or amino group is acylated in alkaline aqueous solution. The copper ion was originally precipitated with hydrogen sulfide,[13] but can also be removed by chelation with 8-hydroxyquinoline as outlined in Scheme 1.[16]



Scheme 1. The classical route to side-chain (meth)acrylic monomers of α-amino acids (here exemplified by serine).[16]

The method has proven successful for the preparation of side-chain (meth)acrylic derivatives of lysine, serine, tyrosine and ornithine,[17] but the procedure is tedious and suffers from poor yields. Therefore, traditional carbamate protecting group chemistry has been used as well, although it works poorly since yields are severely eroded in the workup and purification/crystallization of the intermediate Boc-protected amino acids and the final products (Scheme 2).

One amino acid is noticed for its peculiar absence in the preparation of the side-chain (meth)acrylates, namely hydroxyproline, for which these traditional methods failed for us. Instead of the archetypical alkaline Schotten–Baumann acylation procedures, i.e. of densely protected derivatives with acyl chloride and Et_3N, Et*i*Pr_2N, pyridine, DMAP,



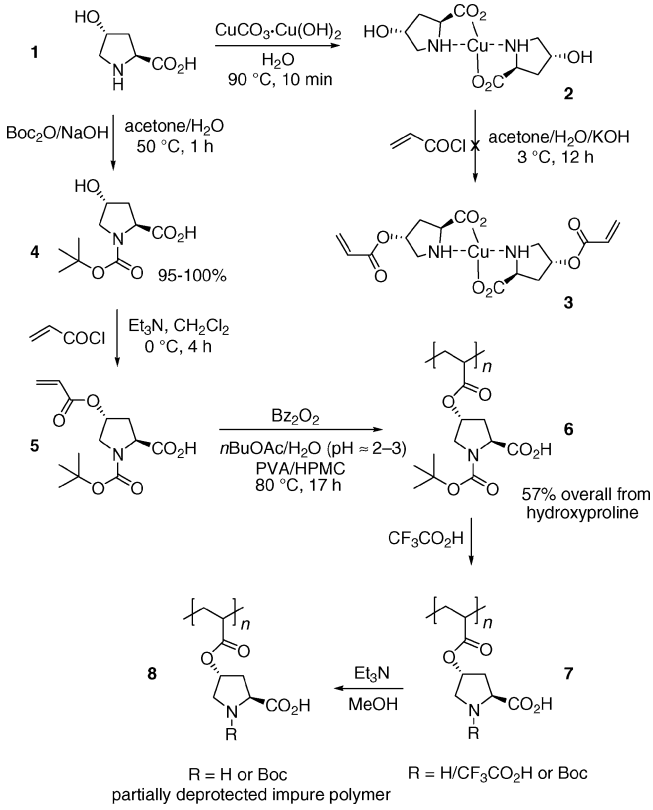
Scheme 2. Use of carbamate protection to prepare side-chain (meth)acrylic monomers of α-amino acids (here exemplified by serine).[15]

K_2CO_3 etc. in organic solvents, procedures of abundance in the chemical literature, we turned our attention to the far less common acidic acylation procedures. Acylation under alkaline conditions requires protection of both amino and carboxylic acid functionalities, whereas acidic conditions protect amines by protonation and to a certain degree also carboxylic acids by not deprotonating them. For hydroxyamino acids, both amine protection and selective *O*-acylation could then be provided in one step. In addition, the free protonated amino group would also serve as protection towards any racemisation at the α-carbon atom, a major concern in amino acid chemistry and yet another advantage of the use of non-protected amino acids. In fact, a solution of L-proline in neat CF_3CO_2H did not show any detectable loss at all of optical rotation when left in a polarimeter continuously for more than 7 h. By acylation of hydroxyproline in CF_3CO_2H, with acylating power modulated by addition of catalytic CF_3SO_3H if needed, we could access the *O*-acrylic derivative of hydroxyproline easily on large scale. As an added bonus, we found that by combining this acylation protocol with crystallization of the free amino acid in lower alcohols with propylene oxide, we could access several of the amphiphilic hydroxyproline derivatives already mentioned, compounds with proven performance in organocatalytic reactions,[3] although they until now have been unnecessary complicated to access considering their simplistic nature. These derivatives should now be readily available and could receive renewed interest for use in organocatalysis.

Results and Discussion

We investigated and quickly realised that the conventional methods were unsuited for the preparation of the polymeric *O*-acryloyl-*trans*-4-hydroxy-L-proline (Scheme 3).[13–16] The copper complex of hydroxyproline (**2**) could not be acylated under the aqueous conditions necessary for dissolution of the complex to give any yield of desired product **3** (Scheme 3). This is not unexpected considering the poor results reported for threonine, an amino acid containing secondary alcohol.[11] The secondary

alcohol of hydroxyproline does not seem to have the necessary reactivity as compared to more reactive serine, lysine or ornithine.



Scheme 3. Preparation of partially deprotected polymer by traditional methods.

We also explored the possibility of removing a Boc protecting group after polymerization as outlined in Scheme 3. The Boc-protected *O*-acrylic hydroxyproline **5** could be suspension-polymerized in acidified water to give the fully protected polymer **6** as polymer beads. Although the protected polymer swells/gels efficiently in CF_3CO_2H and especially in formic acid, no conditions could be identified where the polymer was fully deprotected, even when a broad variety of acids and acid/solvent mixtures was tried out at elevated reaction temperatures and/or prolonged reaction times. We could only obtain the partially deprotected polymer **8**, a product we believe to be of little value. One interesting finding of this work was the poor results obtained for acylations under Schotten–Baumann conditions by using acryloyl chloride in combination with highly nucleophilic bases such as pyridine/DMAP. Only hindered ones such as Et_3N performed well.

The Selective *O*-Acylation of Hydroxyproline

The preparation of *O*-acyl derivatives of hydroxyproline, published as part of a broad study on the synthesis of derivatives of proline and hydroxyproline, has been reported to be very difficult.[19] Moreover, the selective acylation of amino alcohols is a thorny and recognized problem. A recent report on a catalytic system for selective *O*-acylation of amino alcohols has caught the attention of the scientific community.[20]

Literature reports of acidic acylations of amino acids are regretfully sparse considering their potential usefulness, but two reports were of useful guidance to us and seemed to have been passed by surprisingly unnoticed in contemporary synthesis, bearing in mind the burst in proline chemistry reported during the recent decade.[21] The first, dating all the way back to 1964, was the preparation of *O*-acetyl derivatives of hydroxyamino acids (hydroxyproline among them) by dissolution of hydroxyamino acids in a mixture of aqueous HCl and acetic acid, addition of a very large amount (ca. 30 equiv.) of acetyl chloride at 0 °C and precipitation of the pure *O*-acetyl hydroxy amino acid as its hydrochloride salt with diethyl ether.[21a] Although very efficient, such a procedure is of little general value as hydroxyproline has very little solubility in most carboxylic acids, and the use of such an excess of acyl chloride is simply not viable for acyl chlorides other than acetyl chloride. By dissolving hydroxyproline in a mixture of aqueous HCl and acrylic acid, and adding large excesses of acryloyl chloride, we observed hardly any conversion at all. Using mixtures of anhydrous acrylic acid and acryloyl chloride gave even less conversion, even at prolonged reaction times and/or high temperatures. Use of formic acid to bring hydroxyproline into solution gave the formate, although pure and in high (>80%) yield, possibly via the mixed anhydride.

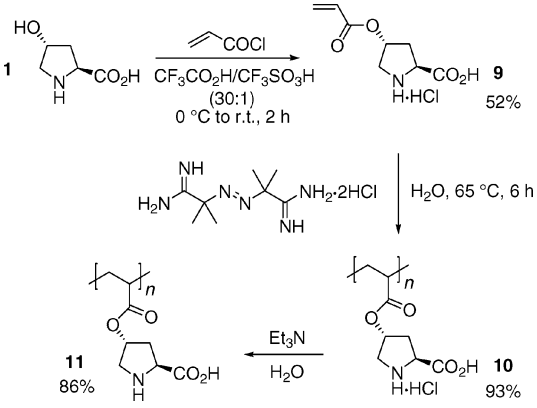
The other useful guidance was a report from 1983 for the preparation of *O*-acyl derivatives of hydroxyproline by acylation in methanesulfonic acid for use in the assembly of peptides with hydrophobic side chains such as butyryl, hexanoyl and lauroyl.[21b] The products were generally obtained as syrupy methanesulfonates with poor crystallinity that are difficult to purify and work up to the free amino acids. Although $MeSO_3H$ is a powerful medium for acidic acylations (H_0 = –7.9 for 100% $MeSO_3H$)[22] and hydroxyproline was quickly acylated with acryloyl chloride to give a syrupy methanesulfonate, further workup proved impossible since the salt could not be purified, and the free amino acid could not be prepared because it quickly reacts with itself by conjugate addition. We also found that acylation in concentrated sulfuric acid (H_0 = –10 for 96–98% H_2SO_4)[22] is possible, but unpredictable, violent and unsafe.

Trifluoroacetic acid has been used as a medium for selective acylation of hydroxy groups in gelatine[23a] and serine.[23b] We found it to be the best medium for acidic acylations of hydroxyproline. Treatment of a concentrated solution of hydroxyproline in CF_3CO_2H with 2 equiv. (found to be the best trade-off between purity/conversion and yield) of acryloyl chloride for 4 h, followed by crystallization from diethyl ether gave the *O*-acryloyl product as its crystalline hydrochloride in 39% yield. Unlike methanesulfonate, which has a high affinity for amino acids, trifluoroacetate seems much less so, which has the benefit of giving the acylation products as (most often) crystalline hydrochloride salts. In addition, we found that we could easily adjust the acylating power of the medium by adding catalytic amounts

of trifluoromethanesulfonic acid. The Hammett acidity function H_0 of 100% CF_3CO_2H is –2.7, whereas that for a solution of only 1.1% (by weight) of CF_3SO_3H in CF_3CO_2H is –7.8 (H_0 = –13.7 for 100% CF_3SO_3H).[24] By using a 1:30 (v/v) mixture of CF_3SO_3H/CF_3CO_2H [corresponding to an approximate 3.5% (w/w) solution, $H_0 \approx$ –8.4],[24] we could obtain the desired product in 52% yield after 2 h.[25]

Large-Scale Preparation of Proline Polymers and Amphiphiles

The advantages of the acidic acylation as described above for large-scale preparations are obvious. *O*-Acryloyl-*trans*-4-hydroxy-L-proline hydrochloride (**9**) was prepared in batches of more than 30 g without any chromatography or protecting groups (Scheme 4). Of course, it is important to note that acrylates do not undergo cationic polymerization. The free amino acid could not, despite repeated attempts, be liberated from its hydrochloride, as it was found to be unstable. This was an unanticipated finding, as we believe the vulnerability of side-chain acrylic amino acid monomers towards conjugate addition does not seem to have been taken into account in any of the previous reports,[11,13–17] and this disadvantage was not present in any other acyl derivative we prepared, as described later.



Scheme 4. Poly(*O*-acryloyl-*trans*-4-hydroxy-L-proline).

As a result, the acrylic monomer had to be polymerized protected in salt form. The water-soluble hydrochloride polymer **10** was easily prepared by polymerization in water with a water-soluble azo initiator. Controlled treatment with Et_3N in aqueous solution caused the desired free amino acid polymer **11** to separate out of solution (Scheme 4). Importantly, all polymerization experiments with the acrylic monomer **9** failed when peroxides (benzoyl peroxide, $K_2S_2O_8$) where used as initiators, even with redox systems at room temperature. Nucleophilic amines tend to react with peroxides.[26]

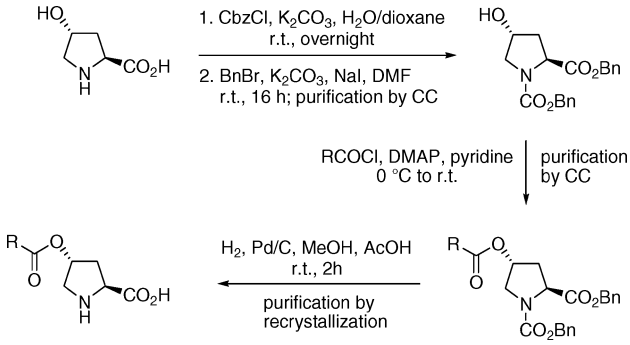
Poly(*O*-acryloyl-*trans*-4-hydroxy-L-proline) is a brittle, glasslike polymer, completely (but slowly) soluble in formamide and mixtures of water and glycerol. To the best of our knowledge, it has also by far the highest proline loading of any immobilized variant of proline reported (5.4 mmol/g), being more comparable to hydroxyproline itself (7.6 mmol/g) than to proline-containing Merrifield resin (typically 0.5–1.5 mmol/g),[4] polyethylene glycol (0.2–0.4 mmol/g)[5] or mesoporous silica (0.5–0.7 mmol/g).[6] Although solubility is limited and the polymer in unmodified form is of limited utility in organocatalysis, experiments with polymer systems prepared from such building blocks are currently under way and will be reported separately. The polymer is fully water-soluble in anionic carboxylate form or the hydrochloride form **10**, these being powerful chelators for copper ions. Addition of aqueous copper(II) salts to aqueous solutions of **10** gives a dark blue complexation, followed by precipitation of a blue coagulate.

The acylation system developed for the *O*-acrylic derivative was used to prepare a series of *O*-acyl derivatives (Table 1). The classical and arduous route to these derivatives is shown in Scheme 5 for Cbz chemistry, according to the general predisposition of amino acid derivative synthesis, even of simple ones, to become trials in multiple Cbz[3d,27] or equally burdensome Boc[4c] attachment/removal and repeated chromatographic purifications.

Table 1. Large-scale preparation of *O*-acyl derivatives of hydroxyproline.

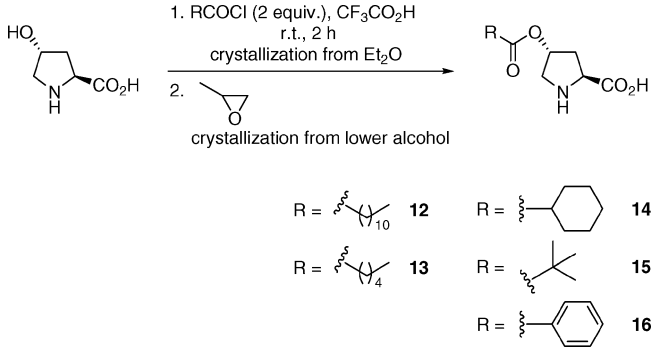
Entry	Derivative	Medium[a]	Acylation yield[b]	Solvent[c]	Total yield[d]
1	**12**	TFA	80–90	MeOH	55
2	**12**	TFA	80–90	EtOH	79
3	**13**	TFA	80–90	EtOH	66
4	**14**	TFA	80–90	EtOH	80
5	**15**	TFA	80–90	EtOH	58
6	**15**	TFA	80–90	*n*PrOH	56
7	**16**	TFA	40–50	EtOH	30[e]
8	**9**	TFA/TFSA	52	none[f]	none[f]

[a] Reaction medium: TFA = CF_3CO_2H; TFSA = CF_3SO_3H. [b] Yields of acylation product (hydrochloride) in percent. Yields should be taken as only indicative since they may vary depending on the purity/conversion that is required for further use. [c] Solvent for crystallization of free amino acid with propylene oxide. [d] Isolated total yields in percent for pure free amino acid *O*-acyl derivative (two steps with two crystallizations), ca. 180 mmol scale (13–45 g of product) for each Entry, by using the conditions in Scheme 6. [e] This compound required an extra recrystallization from H_2O. [f] This product could not be liberated from its hydrochloride salt.



Scheme 5. Classical route to *O*-acyl derivatives of hydroxyproline.[3d,27]

By contrast, direct acidic acylation of hydroxyproline in trifluoroacetic acid gave the *O*-acyl products directly as crystalline hydrochloride salts (from diethyl ether). Treatment of the hydrochloride salts with propylene oxide as acid scavenger[28] in lower alcohols gave the *O*-acylated free amino acid as crystalline pure compounds (Scheme 6). All experiments in Table 1 were undertaken on >20 g scale (of hydroxyproline) and were highly convenient.



Scheme 6. *O*-Acyl derivatives of hydroxyproline by selective *O*-acylation.

As mentioned earlier, the *O*-acrylic derivative as HCl salt **9** was prepared as easily by simply tuning the acylating power of the medium with catalytic amounts of trifluoromethanesulfonic acid, but the free amino acid is now not available because of the marked nucleophilicity of proline towards Michael acceptors such as acrylic esters.[29] Interestingly, the derivative can therefore not easily be carbamate-protected as it decomposes before significant protection has taken place. After all, the sequential additions of amines to acrylates form the typical pathway for construction of dendrimeric frameworks.

Especially the amphiphilic lauroyl derivative **12** and its direct analogues are extremely selective catalysts for intermolecular aldol reactions in aqueous emulsions,[3b,3d,30] and should now be one of the most readily available organocatalysts on multigram scale. Lauroyl derivative **12** has been reported to give nearly quantitative yields and 95–99% *ee* for aldol reactions in W/O or O/W emulsions.[30a] The *O*-pivaloyl derivative **15** and the *O*-benzoyl derivatives **16** have been used as starting materials for chiral cyclic nitrones, versatile intermediates for the synthesis of optically active nitrogen heterocycles.[27a] The *O*-cyclohexylcarbonyl derivative **14** and the *O*-acryloyl derivative **9** (together with its acrylic polymers) have to the best of our knowledge not been reported before and are new through this work.

Most of our extensive investigations into the preparation of *O*-acyl derivatives of hydroxyproline by acidic acylations can be summarized by the following general trends (see Table 1 for some results). Acylations with normal aliphatic carbonyl chlorides generally give good yields of the product hydrochloride, typically 80–90%, depending on the purity required for further use and being very reproducible and virtually unaffected by scale. The yields were under these powerful reaction conditions quite unaffected by the substitution pattern of the aliphatic hydrocarbon chain (i.e. capryol/lauroyl compared to cyclohexylcarbonyl or pivaloyl, Entries 1–5, Table 1). However, the crystallization of the free amino acids from propylene oxide/lower alcohol differs significantly, as can be clearly seen from Table 1. Generally, derivatives containing quite large side chains, i.e. (cyclo)-hexanoyl and upwards, crystallize in high yields, whereas derivatives with shorter chains, such as pivaloyl, are markedly more difficult to crystallize in high yields. The acylation products (as hydrochloride salts) for both types of derivatives may be obtained in approximately equal yields. This pattern is supported by previous literature,[21b] where the smaller acetyl or butyryl derivatives give less overall yields than the larger derivatives. Total yields can also vary significantly according to the lower alcohol utilized (compare for example Entries 1 and 2 in Table 1), although it is our experience that this can be mostly overcome by using the appropriate amount of solvent.

As for conjugated carbonyl chlorides such as acryloyl and benzoyl chloride, yields of acylation product are distinctly lower than for the more reactive normal aliphatic acyl chlorides. For the acrylic derivative **9**, yields and purity were enhanced by addition of CF_3SO_3H, this being especially important for this derivative since it could not be liberated from its hydrochloride. For the benzoyl derivative **16**, overall yield was quite poor since the hydrochloride salt required a treatment with *i*PrOH to achieve good crystallinity and the product a final recrystallization from water. Despite of this, we think it is the preferred method for its preparation as large portions of >10 g material are easily prepared with little work.

As for all derivatives, if additional purity is required, this is easily obtained by recrystallization of the final material from water or lower alcohol (see the Experimental Section for more details on each derivative) with good recovery.

As mentioned earlier, for the simplest *O*-acyl analogues of hydroxyproline, the *O*-formyl derivative is easily available through acylation of hydroxyproline in formic acid with acryloyl chloride (presumably via mixed anhydrides formed in the mixture), and the *O*-acetyl derivative can be most easily accessed by the simple method already reported.[21a]

Conclusions

We have prepared hundreds of grams of *O*-acyl derivatives of hydroxyproline by direct and selective acylation of hydroxyproline in an acidic medium on the basis of CF_3CO_2H. We believe protocols on the basis of acidic acylation are the favoured method for the preparation of *O*-acyl derivatives of hydroxy amino acids. The procedure is free of protecting groups and chromatography, and it is readily adaptable to large scale. As such, it can be just as natural a starting point for chemistry on hydroxyproline as a carbamate protection of the amino group or preparation of a methyl/ethyl ester hydrochloride. The procedure is useful for the preparation of amphiphilic proline derivatives for organocatalysis and novel proline polymers that could have use within fields as disparate as organocatalytical, biochemical, medical or material science research.

Experimental Section

General: All commercially available reagents were used as received, and all solvents were used without further purification. *trans*-4-Hydroxy-L-proline was generously donated by Evonik Degussa GmbH, Exclusive Synthesis & Catalysts. All other reagents were obtained from Sigma–Aldrich. N_2 was utilized only where noted specifically, and magnetic stirring was used throughout. ^1H and ^{13}C NMR spectra were recorded with a Bruker Avance™ DPX-200 spectrometer operating at 200 MHz (^1H) or 50 MHz (^{13}C). Chemical shifts (δ) are reported in ppm and are, unless otherwise noted, reported relative to internal references of the solvent: δ = 3.35/49.9 ppm for CD_3OD and δ = 11.50/164.2 ppm for CF_3CO_2D. For spectra recorded in D_2O, shifts are reported relative to the added internal reference given in the Entry for the compound in question. Electrospray ionization mass spectra were recorded with a Micromass Q-Tof-2™ mass spectrometer. Infrared spectra were recorded with either a Nicolet Magna-IR™ 550 or a Perkin–Elmer Spectrum™ One FTIR spectrometer. Melting points were determined with a Stuart® SMP3 melting point apparatus. Gel-permeation chromatography (GPC) was conducted by Polymer Standards Service (PSS), Mainz, Germany. Analysis conditions: Precolumn: PSS-Suprema, 10 μm, 30 Å, i.d. 8.0 × 50 mm; columns: PSS-Suprema, 10 μm, 30 Å, i.d. 8.0 × 300 mm and PSS-Suprema, 10 μm, 1000 Å, i.d. 8.0 × 300 mm; pump: Agilent 1100 HPLC pump; eluent: aqueous phosphate buffer (11.88 g/L Na_2HPO_4); calibration: poly(acrylic acid), sodium salt; flow-rate: 1.0 mL/min; injection: Agilent 1100 autosampler with 50 μL inject volume; temperature: 23 °C; detector: agilent 1100 RI; calculation: PSS-WinGPC Version Unity 7.20.

Warning: Although we have never suffered any problems with these procedures, it is important to note that acyl chlorides should not be added to the CF_3CO_2H/hydroxyproline solution on large scale before it has cooled to the appropriate temperature (room temperature or below depending on the reactivity of acyl chloride), as it then may heat up excessively when stirred at room temperature. In all cases, if necessary, the reaction will very quickly subside when cooled in an ice/water bath (which should always be available). Instead of forced external cooling or heating, we obtained the best results when the reaction mixture during reaction was allowed to follow its natural cycle of heating and cooling.

Important Note: These hydroxyproline-derived amino acids, as is often the case for amino acids, decompose on melting, and accurate values for the melting points can be difficult to determine. For example, the melting point of L-proline has in most cases been reported spread through values all the way from approximately 210 °C[31a] up to 229 °C.[31b] As a result, for consistency and as described in more detail further on, an analytical sample was prepared of each compound by recrystallization from a suitable solvent (given in each Entry) and the sample dried under vacuum over P_2O_5 and used for the characterization. Such a recrystallization is also advisable if the free amino acid is to be stored for longer periods of time.

***O*-Lauroyl-*trans*-4-hydroxy-L-proline (12):** *trans*-4-Hydroxy-L-proline (23.65 g, 180 mmol) was dissolved in CF_3CO_2H (100 mL) by stirring at room temperature for 15 min. The solution was cooled just below room temperature with an ice/water bath, removed from the bath, and lauroyl chloride (83.4 mL, 361 mmol) was added in one portion (mildly exothermic). The solution was stirred at room temperature for 2 h. Under cooling with an ice/water bath, Et_2O (350 mL) was added carefully to give a fine white precipitate that was vacuum-filtered, washed with Et_2O (150 mL) and dried at room temperature for 42 h to give *O*-lauroyl-*trans*-4-hydroxy-L-proline hydrochloride as a fine white powder. All the hydrochloride salt was dissolved in EtOH (96 vol.-%, 300 mL) by heating. The solution was cooled slightly with an ice/water bath, removed from the bath before any crystallization started, and propylene oxide (30 mL, 429 mmol) was added. Stirring was discontinued and the solution left for crystallization at room temperature for 7 h. The crystals were vacuum-filtered and dried at room temperature to give **12** (44.77 g, 79%) as transparent flat needles. A completely analogous experiment from *trans*-4-hydroxy-L-proline (23.78 g, 181 mmol) and lauroyl chloride (83.8 mL, 362 mmol) with crystallization from MeOH (300 mL) and propylene oxide (30 mL, 429 mmol) gave the same product **12** as transparent flat needles (31.18 g, 55%). A very pure sample for analysis was prepared by recrystallization of this product from MeOH. M.p. 187–189 °C (dec.). $[\alpha]_D^{20}$ = –22.0 (*c* = 0.100, MeOH). ^1H NMR (200 MHz, CF_3CO_2D): δ = 5.55–5.60 (m, 1 H, 4-H), 4.80–4.95 (m, 1 H, 2-H), 3.75–3.96 (m, 2 H, 5-H), 2.70–2.84 (m, 1 H, 3-H), 2.45–2.63 (m, 1 H, 3-H), 2.39 (t, ^3J = 7.6 Hz, 2 H, CH_2), 1.48–1.67 (m, 2 H, CH_2), 1.09–1.35 (m, 16 H, 8 × CH_2), 0.70–0.80 (m, 3 H, Me) ppm. ^{13}C NMR (50 MHz, CF_3CO_2D): δ = 180.3, 174.4, 75.8, 61.6, 54.9, 36.9, 36.3, 34.0, 31.6, 31.5, 31.4, 31.3, 31.1, 31.0, 26.7, 24.5, 14.9 ppm. This is a known compound with spectroscopic properties in accordance with those reported.[3d,21b]

***O*-Caproyl-*trans*-4-hydroxy-L-proline (13):** Exactly as for the *O*-lauroyl derivative **12**, *O*-caproyl derivative **13** was prepared from *trans*-4-hydroxy-L-proline (23.65 g, 180 mmol) and caproyl chloride (49.7 mL, 360 mmol) in CF_3CO_2H (100 mL) to give *O*-caproyl-*trans*-4-hydroxy-L-proline hydrochloride as a fine white powder. All the hydrochloride salt was crystallized the same way as for **12** with EtOH (96 vol.-%, 55 mL) and propylene oxide (30 mL, 429 mmol) at room temperature for 7 h, filtered and dried to give **13** (27.33 g, 66%). A very pure sample for analysis was prepared by recrystallization of this product from water to give **13** as long transparent flat needles. M.p. 201–203 °C (dec.). $[\alpha]_D^{20}$ = –27.4 (*c* = 0.113, MeOH). ^1H NMR (200 MHz, CF_3CO_2D): δ = 5.55–5.65 (m, 1 H, 4-H), 4.85 (dd, ^3J = 10.3 and 8.1 Hz, 1 H, 2-H), 3.90 (dd, ^3J = 13.7 and 4.0 Hz, 1 H, 5-H), 3.79 (d, ^3J = 13.7 Hz, 1 H, 5-H), 2.77 (dd, ^3J = 15.0 and 8.1 Hz, 1 H, 3-H), 2.54 (ddd, ^3J = 15.0, 10.3 and 4.8 Hz, 1 H, 3-H), 2.38 (t, ^3J = 7.5 Hz, 2 H, CH_2), 1.45–1.66 (m, 2 H, CH_2), 1.10–1.34 (m, 4 H, 2 × CH_2), 0.70–0.83 (m, 3 H, Me) ppm. ^{13}C NMR (50 MHz, CF_3CO_2D): δ = 180.3, 174.4, 75.9, 61.7, 55.0, 36.9, 36.3, 33.2, 26.4, 24.0, 14.5 ppm. This is a known compound with spectroscopic properties in accordance with those reported.[3d,21b]

***O*-Cyclohexylcarbonyl-*trans*-4-hydroxy-L-proline (14):** *trans*-4-Hydroxy-L-proline (23.62 g, 180 mmol) was dissolved in CF_3CO_2H (100 mL) by stirring at room temperature for 15 min. The solution was cooled to 5 °C with an ice/water bath, removed from the bath, and cyclohexanecarbonyl chloride (49.0 mL, 361 mmol) was added in one portion (mildly exothermic). The solution was stirred at room temperature for 2 h. Under cooling with an ice/water bath, Et_2O (350 mL) was added carefully to give a fine white precipitate that was vacuum-filtered, washed with Et_2O (150 mL) and dried at room temperature for 21 h to give *O*-cyclohexylcarbonyl-*trans*-4-hydroxy-L-proline hydrochloride as a white powder. All the hydrochloride salt was dissolved in EtOH (96 vol.-%, 250 mL) by heating. The solution was cooled to approximately room temperature with an ice/water bath, removed from the bath, and propylene oxide (30 mL, 429 mmol) was added. Stirring was discontinued and the solution left for crystallization at room temperature for 7 h. The crystals were vacuum-filtered and dried at room temperature to give **14** (34.63 g, 80%) as colourless crystals. A very pure sample for analysis was prepared by recrystallization of this product from

water. M.p. 218–220 °C (dec.). $[\alpha]_D^{20}$ = –28.6 (*c* = 0.112, MeOH). ^{1}H NMR (200 MHz, CF_3CO_2D): δ = 5.59 (br. s, 1 H, 4-H), 4.78–4.93 (m, 1 H, 2-H), 3.91 (dd, ^3J = 13.6 and 4.0 Hz, 1 H, 5-H), 3.79 (d, ^3J = 13.6 Hz, 1 H, 5-H), 2.76 (dd, ^3J = 15.0 and 8.0 Hz, 1 H, 3-H), 2.56 (ddd, ^3J = 15.0, 10.3 and 4.8 Hz, 1 H, 3-H), 2.27–2.46 (m, 1 H, cyclo-CH), 1.60–1.95 (m, 5 H, cyclo-CH_2), 1.00–1.48 (m, 5 H, cyclo-CH_2) ppm. ^{13}C NMR (50 MHz, CF_3CO_2D): δ = 182.3, 174.4, 75.7, 61.7, 55.0, 45.9, 37.0, 30.9, 30.8, 27.1, 27.04/26.97 ppm. IR (KBr): $\tilde{\nu}$ = 3026, 2947, 2929, 2857, 1735, 1629 cm^{-1}. HRMS (ESI): calcd. for [$C_{12}H_{19}NO_4$ + H] 242.1392, found 242.1394. $C_{12}H_{19}NO_4$ (241.28): calcd. C 59.73, H 7.94, N 5.81; found C 59.81, H 8.05, N 5.65.

***O*-Pivaloyl-*trans*-4-hydroxy-L-proline (15):** *trans*-4-Hydroxy-L-proline (23.69 g, 181 mmol) was dissolved in CF_3CO_2H (100 mL) by stirring at room temperature for 15 min. The solution was cooled just below room temperature with an ice/water bath, removed from the bath, and pivaloyl chloride (44.5 mL, 362 mmol) was added in one portion (mildly exothermic). The solution was stirred at room temperature for 2 h. Under cooling with an ice/water bath, Et_2O (350 mL) was added carefully to give a fine white precipitate that was vacuum-filtered, washed with Et_2O (150 mL) and dried at room temperature for 17 h to give *O*-pivaloyl-*trans*-4-hydroxy-L-proline hydrochloride as a white powder. All the hydrochloride was dissolved in *n*PrOH (350 mL) by heating. The solution was cooled to approximately room temperature with an ice/water bath, removed from the bath, and propylene oxide (30 mL, 429 mmol) was added. Stirring was discontinued and the solution left for crystallization at room temperature for 5 h. The crystals were vacuum-filtered and dried at room temperature to give **15** (21.67 g, 56%) as white fibrous crystals. A completely analogous experiment from *trans*-4-hydroxy-L-proline (23.66 g, 180 mmol) and pivaloyl chloride (44.4 mL, 361 mmol) with crystallization from EtOH (96 vol.-%, 150 mL) and propylene oxide (30 mL, 429 mmol) gave the same product **15** as white fibrous crystals in two portions (22.46 g combined, 58%), crystallization of the second portion initiated with added Et_2O. A very pure sample for analysis was prepared by recrystallization of this product from *n*PrOH. M.p. 207–209 °C (dec.). $[\alpha]_D^{20}$ = –30.6 (*c* = 0.111, MeOH). ^{1}H NMR (200 MHz, D_2O, reported relative to added formamide at δ = 8.06 ppm): δ = 5.47 (t, ^3J = 4.2 Hz, 1 H, 4-H), 4.35 (dd, ^3J = 10.6 and 7.8 Hz, 1 H, 2-H), 3.71 (dd, ^3J = 13.4 and 4.2 Hz, 1 H, 5-H), 3.54 (d, ^3J = 13.4 Hz, 1 H, 5-H), 2.58 (dd, ^3J = 14.6 and 7.8 Hz, 1 H, 3-H), 2.32 (ddd, ^3J = 14.6, 10.6 and 4.2 Hz, 1 H, 3-H), 1.21 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (50 MHz, D_2O, reported relative to added formamide at δ = 167.92 ppm): δ = 181.7, 174.6, 75.1, 61.4, 51.9, 39.7, 36.3, 27.3 ppm. This is a known compound with spectroscopic properties in accordance with those reported.[27a]

***O*-Benzoyl-*trans*-4-hydroxy-L-proline (16):** *trans*-4-Hydroxy-L-proline (23.64 g, 180 mmol) was dissolved in CF_3CO_2H (100 mL) by stirring at room temperature for 15 min. The solution was cooled just below room temperature with an ice/water bath, removed from the bath, and benzoyl chloride (41.8 mL, 360 mmol) was added in one portion (mildly exothermic). The solution was stirred at room temperature for 2 h. Under cooling with an ice/water bath, Et_2O (350 mL) was added carefully. Stirring was discontinued, and the sticky precipitate was allowed to settle for 15 min. The clear supernatant was decanted, and *i*PrOH (100 mL) was added to the solid residue. Vigorous stirring at near reflux gave a fine white suspension. When it became homogeneous, it was cooled with an ice/water bath, and Et_2O (200 mL) was added whilst stirring. The resulting suspension was vacuum-filtered, washed with Et_2O (50 mL) and dried at room temperature for 16 h to give *O*-benzoyl-*trans*-4-hydroxy-L-proline hydrochloride as a fine white powder. All the hydrochloride salt was dissolved in EtOH (96 vol.-%, 100 mL) by heating. The solution was cooled to approximately room temperature in an ice/water bath, removed from the bath, and propylene oxide (20 mL, 286 mmol) was added. Stirring was discontinued and the solution left for crystallization at room temperature for 7 h. The crystals were vacuum-filtered and dried at room temperature to give **16** as small colourless crystals. The product was recrystallized from boiling water (160 mL) to give **16** as colourless crystals (12.77 g, 30% overall). M.p. 217–219 °C (dec.). $[\alpha]_D^{20}$ = –6.4 (*c* = 0.173, MeOH). ^{1}H NMR (200 MHz, CF_3CO_2D): δ = 7.90–8.05 (m, 2 H, Ph-H), 7.53–7.68 (m, 1 H, Ph-H), 7.35–7.50 (m, 2 H, Ph-H), 5.87 (br. s, 1 H, 4-H), 5.04 (dd, ^3J = 10.3 and 8.1 Hz, 1 H, 2-H), 4.05 (br. s, 2 H, 5-H), 3.02 (dd, ^3J = 15.0 and 8.1 Hz, 1 H, 3-H), 2.72 (ddd, ^3J = 15.0, 10.3 and 4.8 Hz, 1 H, 3-H) ppm. ^{13}C NMR (50 MHz, CF_3CO_2D): δ = 174.5, 171.7, 137.7, 132.2, 131.2, 129.5, 76.5, 61.9, 55.2, 37.1 ppm. This is a known compound with spectroscopic properties in accordance with those reported.[21b,27a]

***O*-Acryloyl-*trans*-4-hydroxy-L-proline Hydrochloride (9):** Powdered *trans*-4-hydroxy-L-proline (38.17 g, 291 mmol, dried at 65 °C for 21 h) was added in small portions over a period of 5–10 min to CF_3CO_2H (90 mL) with vigorous stirring under cooling with an ice/water bath to give a viscous solution (leaving some small pieces of undissolved material). After 5 min, CF_3SO_3H (3.0 mL, 34.4 mmol) was added, followed 5 min later by acryloyl chloride (46.0 mL, 569 mmol). The reaction flask was removed from the ice/water bath, and the reaction mixture was stirred at room temperature (mildly exothermic). After 20 min, extra CF_3CO_2H (10 mL) was added to give a colorless and clear solution, and stirring was continued for 1 h and 40 min (to give a total of 2 h of reaction time at room temperature). The reaction flask was then cooled with an ice/water bath, and Et_2O (540 mL) was added under vigorous stirring over a period of 20 min, slowly at first. The resulting white suspension was stirred at 0–5 °C for 15 min after completed addition and then vacuum-filtered, the crystals were washed with several portions of Et_2O and dried at room temperature in a ventilated hood for 24 h to give **9** (33.26 g, 52%) as a fine white powder, used for the next step without further purification. A pure sample for analysis was prepared by recrystallization of this product from boiling acetone containing a small amount of water to give **9** as transparent crystals. M.p. 212–214 °C (dec.). $[\alpha]_D^{20}$ = –13.1 (*c* = 0.137, MeOH). ^{1}H NMR (200 MHz, CD_3OD): δ = 6.53 (dd, ^3J = 17.2 and 1.7 Hz, 1 H, acrylic H), 6.25 (dd, ^3J = 17.2 and 10.3 Hz, 1 H, acrylic H), 6.01 (dd, ^3J = 10.3 and 1.7 Hz, 1 H, acrylic H), 5.53–5.61 (m, 1 H, 4-H), 4.68 (dd, ^3J = 10.5 and 7.9 Hz, 1 H, 2-H), 3.80 (dd, ^3J = 13.3 and 4.6 Hz, 1 H, 5-H), 3.59 (dt, ^3J = 13.3 and 1.5 Hz, 1 H, 5-H), 2.69 (ddt, ^3J = 14.6, 7.9 and 1.6 Hz, 1 H, 3-H), 2.52 (ddd, ^3J = 14.6, 10.5 and 4.9 Hz, 1 H, 3-H) ppm. ^{13}C NMR (50 MHz, CD_3OD): δ = 171.4, 167.3, 133.9, 129.7, 75.0, 60.5, 53.2, 36.7 ppm. IR (KBr): $\tilde{\nu}$ = 3440, 1722, 1635, 1619 cm^{-1}. HRMS (ESI): calcd. for [$C_8H_{11}NO_4$ + H] 186.0766, found 186.0770. $C_8H_{12}ClNO_4$ (221.64): calcd. C 43.35, H 5.46, N 6.32; found C 43.12, H 5.45, N 6.21.

Poly(*O*-acryloyl-*trans*-4-hydroxy-L-proline) (11): *O*-Acryloyl-*trans*-4-hydroxy-L-proline hydrochloride (11.13 g, 50.2 mmol) was dissolved in deaerated water (35 mL) together with 2,2′-azobis(2-amidinopropane) dihydrochloride (114 mg, 0.42 mmol) by swirling. The reaction flask was purged with N_2 for 5 min and then placed into a bath of glycerol. The bath was heated to 65 °C and kept at this temperature for 6 h while keeping the reaction mixture under N_2. The viscous solution was cooled to room temperature and then poured into 2-propanol (300 mL) whilst stirring. The separated lump of polymer was isolated and sequentially submerged into more 2-propanol (200 mL), then Et_2O (200 mL) and finally into

more Et_2O (200 mL), each time allowing the piece of polymer to sit for some time with occasional stirring. The white polymer was separated once more and dried under vacuum in a desiccator over concentrated H_2SO_4 at room temperature for 72 h and then in air at the same temperature for 2 d to give poly(*O*-acryloyl-*trans*-4-hydroxy-L-proline hydrochloride) (**10**, 10.36 g, 93%) as a crystalline solid. ^1H NMR (D_2O, 200 MHz, reported relative to residual 2-propanol at δ = 4.02 ppm): δ = 5.45–5.65 (m, 1 H, 4-H), 4.59 (t, ^3J = 8.4 Hz, 1 H, 2-H), 3.75–3.95 (m, 1 H, 5-H), 3.55–3.75 (m, 1 H, 5-H), 2.35–2.80 (m, 3 H, 2 × 3-H and H on acrylic backbone), 1.55–2.30 (m, 2 H, 2 × H on acrylic backbone) ppm. IR (KBr): $\tilde{\nu}$ = 3429, 2968, 1732, 1632 cm^{-1}. Molecular weight distribution (M_n = 29600, M_w = 686000) was determined by GPC analysis in aqueous phosphate buffer by using the sodium salt of poly(acrylic acid) as calibration standard. A portion of poly(*O*-acryloyl-*trans*-4-hydroxy-L-proline hydrochloride) (**10**, 5.11 g) was dissolved in water (40 mL) at room temperature to give a clear viscous solution, and Et_3N was added dropwise whilst stirring with a spatula. A white piece of polymer started to separate from the solution and the addition was continued until the pH of the aqueous phase stabilized at ca. 6 (close to the isoelectric point for hydroxyproline). The polymer was separated and sequentially submerged into another portion of water (100 mL), MeOH (100 mL), MeOH (50 mL) and finally Et_2O (50 mL), each time allowing the polymer to sit for some time with occasional stirring. The polymer was separated once more and dried under vacuum in a desiccator over concentrated H_2SO_4 at room temperature for 26 h and then in air at the same temperature for 24 h to give poly(*O*-acryloyl-*trans*-4-hydroxy-L-proline) (**11**, 3.67 g, 86%) as a transparent and brittle, crystalline solid (soluble in formamide and water/glycerol mixtures). IR (KBr): $\tilde{\nu}$ = 3436, 2978, 2943, 1738, 1634 cm^{-1}. Elemental analysis: C 46.55, H 5.52, N 6.83.

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