

Mild alkaline hydrolysis of hindered esters in non-aqueous solution

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Dedicated to Professor Dieter Seebach on the occasion of his 80th birthday

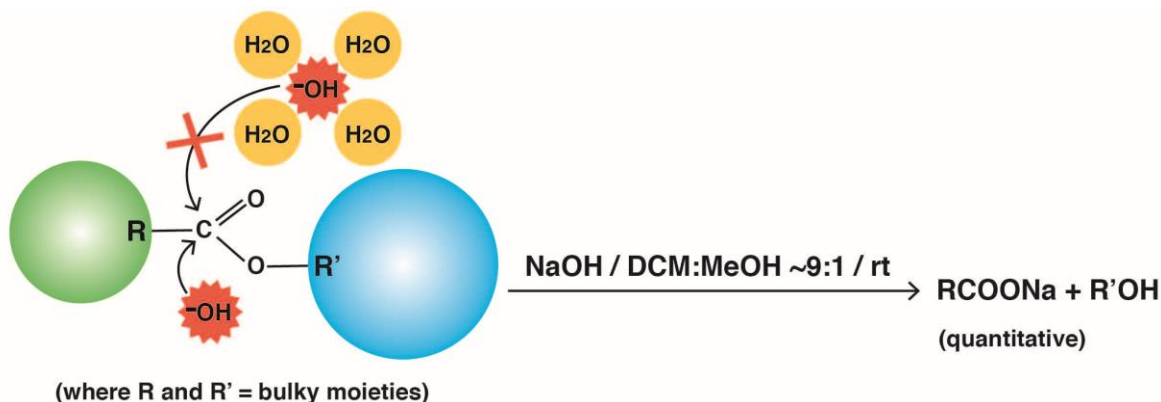
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Abstract

Sterically hindered esters of carboxylic acids, which are considered very resistant to saponification, were rapidly and efficiently saponified in a non-aqueous medium using NaOH in MeOH/CH₂Cl₂ (1:9) at room temperature. Furthermore, this reaction protocol was extended and successfully applied to the hydrolysis of tosylates and *N*-tosyl indoles.



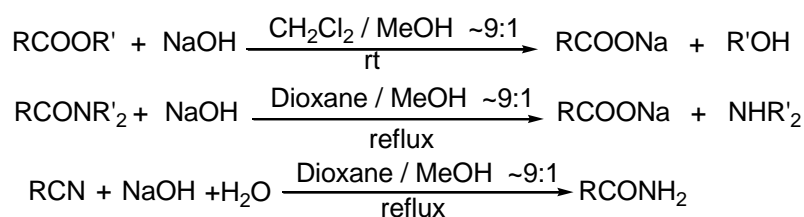
Keywords: *t*-Butyl esters; non-aqueous conditions; saponification, hindered esters; tosylates; *N*-tosyl indoles

Introduction

Alkaline hydrolysis of an ester is one of the most extensively investigated reactions. Typical methods for saponification involve the use of aqueous solutions of water-miscible solvents, large excesses of hydroxides, long reaction times, and high temperatures. The reaction rate is altered by steric and electronic effects^{1,2} as well as the reaction solvent³⁻⁵ due to interactions of the protic solvent with the hydroxyl anions. Solvation of the anions by water molecules through hydrogen bonding⁶⁻⁸ increases the energy barrier for the reactions. Replacing the traditional polar protic solvents with non-polar aprotic solvents can also exert a profound effect on the reaction rates.

The development of a mild-ester hydrolysis method is of great importance, especially in the synthesis of complex molecules, the chemistry of natural compounds, and total synthesis. A need exists for a versatile and simple process whereby esters may be hydrolysed without heating or exposure to extreme pH values. Crowded esters, in particular, typically afford low yields due to steric hindrance which makes carbonyl attack difficult.

In a previous work, we reported the alkaline hydrolysis of esters in non-aqueous reaction medium under very mild conditions,⁹ including short reaction times at room temperature, and the use of a low concentration of alkali in MeOH/CH₂Cl₂ (1:9) as a solvent. We have also developed a mild protocol for the alkaline hydrolysis of secondary and tertiary amides¹⁰ to the corresponding acids and amines, while nitriles are converted to primary amides (Scheme 1).



Scheme 1. Alkaline hydrolysis of esters and amides and hydration of nitriles in non-aqueous conditions.

A plausible mechanistic process was proposed^{9,10} based on the well-established observation that hydroxide anions, when poorly solvated, attack the carbonyl groups of the esters or of the amides much more easily than the ordinarily strongly-solvated hydroxyl anions in an aqueous environment.

This method has subsequently been used to prepare sensitive compounds in excellent yields, without racemization, isomerization or other undesirable reactions. It is worth noting also that, in some of these cases, conventional methods for hydrolysis of carboxylic esters in aqueous solution did not take place under basic conditions.¹¹⁻¹⁹ Moreover, the method has been applied to the hydrolysis of several sulfonates.²⁰

Very recently, in an attempt to hydrolyse a methyl-ester moiety on a substrate also possessing a *tert*-butyl ester group using our methodology, we were surprised to find that the *tert*-butyl group was also removed. This observation motivated us to investigate further our reaction system, using a series of sterically-hindered carboxylic esters to extend our previously-published methodology and further demonstrate its applicability to a large number of compounds.

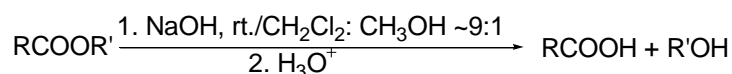
To the best of our knowledge, there are several reports on the alkaline hydrolysis of hindered esters in non-aqueous conditions.²¹⁻²⁵ These include, among others, the use of potassium *tert*-butoxide in DMSO,²¹⁻²² the use of a KOH complex in the presence of a phase-transfer catalyst,²³ and the transesterification of

sterically-hindered steroid esters to methyl esters in MeOH/Et₃N under high-pressure conditions.²⁴ Cleavage of *tert*-butyl benzoates has been attempted with NaH in DMF or, alternatively, with KOH/THF/crown ethers at high temperature.²⁵ The *tert*-butyl moiety is widely used as a valuable protecting group for acids and alcohols in organic synthesis, since *tert*-butyl esters are remarkably stable to basic hydrolysis, but labile to acid hydrolysis.

Herein, we report, for the first time, the applicability and potency of our method in the alkaline hydrolysis of hindered esters and tosylates with very good yields.

Results and Discussion

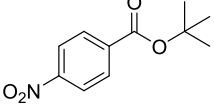
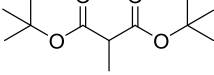
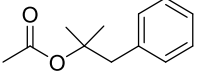
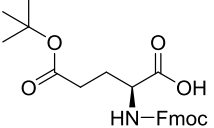
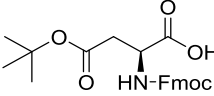
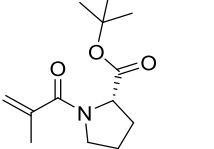
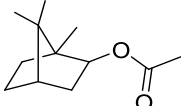
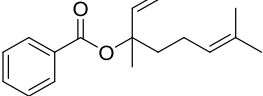
In order to establish our methodology, a diverse set of hindered esters was selected and submitted to saponification, including esters of crowded secondary or tertiary alcohols, some of them natural products or their derivatives. For an approximate experimental comparison, parallel reactions were performed under classical conditions using 0.3 N NaOH in 80% MeOH/H₂O at rt (Scheme 2).

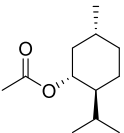
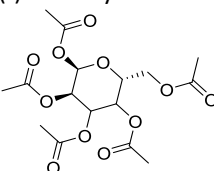
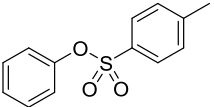
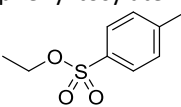
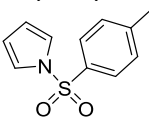
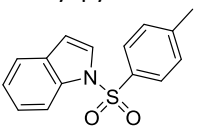
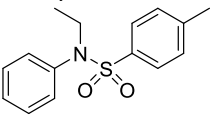
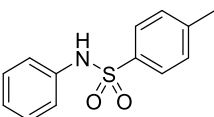


Scheme 2. General reaction scheme for study of saponification of diverse hindered esters using new protocol.

The study was extended to other substrates including several tosylates which were submitted to the mild-alkaline hydrolysis according to this protocol. The reaction progress was monitored by TLC. After hydrolysis, the resulting alcohol or acid or both can be recovered. The conversion reactions were nearly quantitative, as revealed by the TLC analysis, unless otherwise noted. The results are summarized in Table 1. In all cases, the reactions gave rapidly the acid and/or alcohol hydrolysis products quantitatively in high purity (isolated yields 80-96%) by the use of 0.3 N NaOH in 10% MeOH/CH₂Cl₂ at rt. Sodium hydroxide was used in excess, in most of the cases, in a ratio of ester/NaOH of 1:3. By addition of the methanolic solution of NaOH to the ester (or other substrate) dissolved in dichloromethane, a white, finely-dispersed precipitate of sodium salt begins to form slowly and increases over time. For some entries (**6**, **7**, **12**, **14**, and **15**), yields were not determined (nd), as the reaction products were soluble in water and/or of not special interest. Yields are not shown in column 2 of Table 1 since our primary interest was the comparison of the reaction-completion times using both methods, as observed by TLC analysis. Obviously, the classical procedure was very much slower when the esters were sterically hindered.

Table 1. Results of examples for the alkaline hydrolysis of hindered esters and other substrates.

Entry	Ester	Ester/ NaOH (mmol/mmol)	Reagents, solvents, conditions ^a	
			0.3 N NaOH/DCM:MeOH (9:1) ^b Time, ^c yield, temp., mp (lit.mp)	0.3 N NaOH/H ₂ O:MeOH (2:8) ^b Time, ^c temp.
1	 <i>t</i> -butyl <i>p</i> -nitrobenzoate	1:3	5 h 30 min, 93% (RCOOH), rt mp 236-239 (lit. 237-240) °C ²⁶	30 h, rt
2	 di- <i>t</i> -butyl 2-methylmalonate	1:4	3 h, 84% (RCOOH), rt mp 127-129 (128-130) °C ²⁶	>28 h, rt ^e
3	CH ₃ (CH ₂) ₁₃ CH ₂ COOCMe ₃ <i>t</i> -butyl palmitate	1:3	25 min, 95% (RCOOH), rt mp 59-61 (61-62.5) °C ²⁶	~30 h, rt
4	CH ₃ (CH ₂) ₁₃ CH ₂ COOCHPh ₂ diphenylmethyl palmitate	1:3	20 min, 94% (R'OH), rt mp 64-66 (65-67) °C ²⁶	3 h, rt
5	 dimethylbenzylcarbonyl acetate	1:3	3 h 30 min, 96% (R'OH), rt Viscous liquid	~30 h, rt
6	 Fmoc-L-Glu(O <i>t</i> Bu)-OH	1:5	4.5 h, nd, ^d rt	~48 h, rt
7	 Fmoc-L-Asp(O <i>t</i> Bu)-OH	1:5	5 h, nd, rt	~50 h, rt
8	 <i>t</i> -butyl <i>N</i> -methacryloyl-L-prolinate	1:3	1 h, 80% (RCOOH), 30 °C viscous	~25 h, 30 °C
9	 isobornyl acetate	1:3	2 h 30min, 91% (R'OH), rt mp 210-213 (212-214) °C ²⁶	~24 h, rt
10	 linalyl benzoate	1:4	5 h 30 min, 93% (R'OH), 30 °C	~3 d, 30 °C

11		1:3	45 min, 95% (R'OH), rt mp 41-43 (41-44) °C ²⁶	~ 24 h, rt
	(-)-menthyl acetate			
12		1:10	10-15 min, nd., rt	21 h, rt
	α -D(+)-glucose pentaacetate			
13		1:3	3 h 45 min, 80% (PhOH), rt 50 min, 30 °C	~4 d, rt ~9 h, 30 °C
	phenyl tosylate			
14		1:3	~6 h, nd, 30 °C	~20 h, 30 °C
	ethyl tosylate			
15		1:4	~7 h, nd, 30 °C	>30 h, 30 °C ^e
	N-tosyl pyrrole			
16		1:4	4 h 30 min, 82% (indole), 30 °C, mp 50-52 (51-54) °C ²⁶	>24 h, 30 °C ^e
	N-tosyl indole			
17		1:3	No reaction	No reaction
	N-ethyl-N-tosyl-aniline			
18		1:3	Salt formation	Salt formation
	N-tosyl-aniline			

^aReaction conditions: ester (1 mmol), 0.3 N NaOH (3 mmol), solvent (10 mL, CH₃OH:CH₂Cl₂ 1:9) or (10 mL, CH₃OH:H₂O 8:2). ^bEach mL of the solution corresponds to 0.3 mmol of NaOH. The same volume of the solvent is used for both solvent systems. ^cMonitored by TLC until the starting material was consumed. ^dnd: not determined. ^eIncomplete reaction (~ 50%).

It is clear from all of the examples that our hydrolysis protocol is efficient, and much faster with milder conditions than conventional methods, producing high yields of the desired products. In addition, it is particularly useful to note that the precipitated sodium carboxylates or tosylates can be easily separated by filtration or extraction. In selected cases (**8**, **10**, **13-16**), the temperature was maintained at ~30 °C to speed up slow reactions.

The ^1H NMR data of the isolated hydrolysis products were identical with those of authentic samples. The disappearance of the proton peaks attributed to the acid or alcohol moieties of the ester following hydrolysis provided evidence that the hydrolysis reactions were complete. The asterisk denotes the peaks that disappear after hydrolysis (see Supplementary Material, Figure S5-S16).

The optical purity of optically-active compounds was determined by comparison with reported values. Specific rotation and HPLC analyses have proven the lack of racemization, thus establishing the non-racemization feature of the saponification protocol (Supplementary Material, Figure S1-S4).

Specifically, the saponification of *tert*-butyl *p*-nitrobenzoate, di-*tert*-butyl 2-methylmalonate, the two palmitates, and dimethylbenzylcarbonyl acetate (**1-5**) proceeded relatively rapidly. The racemic mixtures of isobornyl acetate and linalyl benzoate (**9, 10**) were saponified after 2.5 and 5.5 hours, instead of 1 and 3 days, respectively.

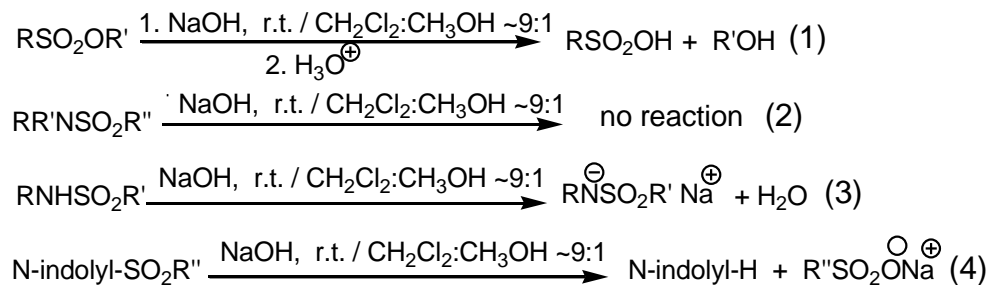
The β - and γ -*tert*-butyl esters of *N*-fluorenylmethyloxycarbonyl (Fmoc) amino acids *N*-Fmoc-L-glutamic and *N*-Fmoc-L-aspartic, **6** and **7**, respectively (specific optical rotation for *N*-Fmoc-L-Glu-OH: $[\alpha]_{\text{D}}^{20}$ -5, *c* 1 in AcOH/H₂O, 4:1, and for *N*-Fmoc-L-Asp-OH: $[\alpha]_{\text{D}}^{20}$ -24, *c* 1 in DMF), were hydrolysed without racemization, and with simultaneous Fmoc-deprotection (specific optical rotation for L-Glu-OH: +30, lit. $[\alpha]_{\text{D}}^{20}$ +31.5, *c* 2 in 5N HCl²⁶ and for L-Asp-OH: +24, lit. $[\alpha]_{\text{D}}^{20}$ +25, *c* 2 in 5N HCl).²⁶ HPLC results (Figure S1 and S2) showed the presence of one product after the alkaline hydrolysis of both, Fmoc-L-Asp(-OtBu)-OH and Fmoc-L-Glu(-OtBu)-OH. The enantiomeric purity was determined by HPLC analysis using Chirobiotic T column (water/methanol/formic acid: 30/70/0.02, flow rate 1.0 mL/min). The L-Asp was eluted at 4.32 min, while the D-Asp was eluted at 5.28 min (Figure S1. A. and B). The L-Glu and D-Glu were eluted at 4.23 and 5.43 min (Figure S2. A. and B), respectively. These results clearly suggest that their saponification took place with retention of configuration.

Importantly, *t*-butyl *N*-methacryloyl-L-prolinate (**8**) was saponified after 1 hour to afford *N*-methacryloyl-L-proline, without hydrolysis of the amide bond, instead of 25 h under the classical conditions. The *N*-methacryloyl-L-proline had a specific rotation of -136.2, lit. $[\alpha]_{\text{D}}^{20}$ -137.8, *c* 1.2 in chloroform,²⁷ confirming the absence of racemization. HPLC analysis showed the presence of only one product (enantiomer) after the alkaline hydrolysis of the ester during all of the different flows (Figure S3 and S4). The ^1H NMR data of *N*-methacryloyl-L-proline and its *t*-butyl ester are consistent with the *cis* and *trans* isomers, existing in solution, due to restricted rotation about the amide bond, and depending on the solvent. In chloroform, the *trans* isomer is favored, because of the γ -turn, the intramolecular H-bonding in the acid form between the CO oxygen and the COOH hydrogen (*trans* 91%, *cis* 9%), while the *cis* isomer of the *t*-butyl ester increases to about 33% (*trans* about 67%), (^1H NMR spectrum, Figure S10).

The alkaline hydrolysis of optically active (-)-menthyl acetate (**11**) was completed in 45 minutes, instead of 24 hours under normal conditions. Based on the ^1H NMR spectrum (Figure S13) and the specific optical rotation of the recovered (-)-menthol {-48, lit. (-)-menthol $[\alpha]_{\text{D}}^{20}$ -50, *c* 10 in ethanol},²⁶ after hydrolysis of the (-)-menthyl acetate, it was concluded that the reaction proceeded without racemization *via* the B_{AC}2 mechanism. The absolute configuration of the carbon atom bearing the OH group of (-)-menthol (1R, 2S, 5R) did not change to give the epimer (+)-neomenthol (1S, 2S, 5R), as verified by its ^1H NMR spectrum, which is different from that of (+)-neomenthol. No inversion of the configuration at C-1 took place during the alkaline hydrolysis. The more characteristic proton (CHOH) of (+)-neomenthol resonates at 4.10 ppm and that of (-)-menthol at 3.41 ppm (^1H NMR spectrum, Figure S13).

We subsequently explored the potential application of our developed protocol to peracetylated glucose (α -D-pentaacetyl glucose). The corresponding D-(+)-glucose was formed, quantitatively, as a mixture of α - and β -anomers within 15 min at rt (**12**); under normal conditions, the reaction was very slow (21 h).

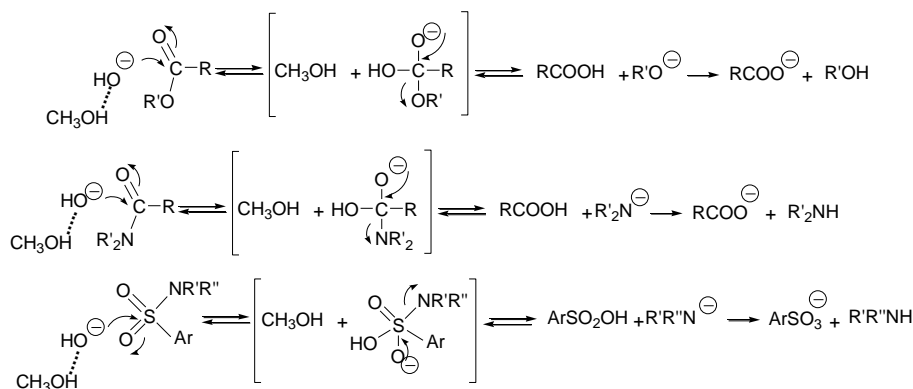
The above methodology was also applied to the hydrolysis of tosylates and *N*-tosyl amides^{28, 29} (**13-18**), (Scheme 3, eq. 1-4).



Scheme 3. Reactions for the alkaline hydrolysis of tosylates and *N*-tosyl amides.

Indole derivatives are extensively explored molecules with significant biological activities, and a wide range of applications. For their synthesis, protection of the indole NH was necessary, followed by removal of the protective group. Sulfonamides, prepared easily with sulfonyl chloride, are between the best nitrogen protective groups. Tosyl group is one such blocking group; its deprotection usually requires harsh conditions. Introduction of a sulfonyl group on the nitrogen of pyrrole, indole and derivatives for *N*-sulfonyl protection, as well as the relatively harsh conditions of alkaline hydrolysis for *N*-sulfonyl deprotection,³⁰ encouraged us to try our alternative method. It is of interest to note that phenyl tosylate (**13**) was completely hydrolysed after ~3.5 h, compared with ~4 d using the classical methodology (and 50 min and ~9 h, respectively, at 30 °C). Ethyl tosylate (**14**) was hydrolysed at 30 °C after 6 h and 20 h, respectively. With our protocol, *N*-tosyl pyrrole (**15**) and *N*-tosyl indole (**16**) were hydrolysed after 7 h and 4.5 h at 30 °C, respectively. Under normal reaction conditions, approximately 50% of the *N*-protected compounds reacted after 30 h and 24 h, respectively (according to TLC). The alkaline hydrolysis of *N*-tosyl-*N*-ethylaniline (**17**) was impossible, even following refluxing with 0.3 N NaOH (6 equiv.) in dioxane/methanol (9:1) for 2 days. On the other hand, *N*-tosyl-aniline (**18**) immediately gave the corresponding sodium salt, due to its acidic proton on N-1. These differences in the reaction completion times are expected, due to the higher electrophilicity of the sulfonyl group of compounds **13** and **16**.

Alkaline hydrolysis has been widely studied, and it is commonly accepted that the majority of the esters are saponified via a two-step B_{AC}2 mechanism.³¹⁻³⁷ In the non-aqueous solvent reaction, unsolvated or “naked” hydroxyl anions approach and attack the carbonyl carbon of the hindered esters much more easily than solvated ions to afford the hydrolysis products (Scheme 4).



Scheme 4. Suggested mechanism for the alkaline hydrolysis in non-aqueous conditions.

Conclusions

In conclusion, our saponification methodology constitutes an advantageous mild, non-racemizing alternative to existing methods. It is shown to be available for the alkaline hydrolysis of crowded esters which are normally resistant to saponification, and for detosylation of tosylates and *N*-tosyl protected pyrroles and indoles. This protocol may be useful, as well, for other substrates.

Experimental Section

General. All chemicals were obtained from commercial suppliers and used without further purification. TLC plates were from Merck Silica gel 60 F₂₅₄. Optical rotations were measured on an automatic digital polarimeter. ¹H NMR spectra were recorded on a Bruker (AV500 MHz) at ambient temperature, using tetramethylsilane (TMS) as an internal standard. HPLC experiments were performed at 25 °C using a Shimadzu system, consisting of a DGU-20A controller, a LC-20AD pump, a SPD-M20A photodiode-array detector and a CTO-10AS column oven, controlled with Shimadzu Class-VP, version 6, software. Elemental analyses were performed on a Heraeus CHN-Rapid Analyzer. The hydrolysis products are known compounds and were identified by comparison with authentic samples, derived from the pure products suppliers.

General experimental procedure. To a solution of the ester (1 mmol) in CH₂Cl₂ (9 mL) was added a methanolic solution of 3 N NaOH (1 mL, 3 mmol), with the final concentration of the alkali being 0.3 N, and the solvent mixture CH₂Cl₂/CH₃OH (9:1, v/v, 10 mL). Esters bearing more than one ester moiety needed more equivalents of NaOH (Table 1). After stirring, the solution became cloudy and the sodium salt of the carboxylic acid began to precipitate. The progress of the reaction was monitored by thin layer chromatography (TLC). The mixture was stirred until the ester was consumed (Table 1), the solvents were then removed under vacuum, the residue was diluted with water (10 mL) and extracted with ethyl acetate or diethyl ether (2x20 mL) to isolate the water-insoluble alcohol, and/or to remove unreacted ester. The aqueous phase was cooled, acidified to pH ~2 with dilute HCl and extracted with AcOEt (2x20 mL). The combined organic layers were dried (Na₂SO₄) and the solvent removed to afford the acid. Alternatively, the RCOONa precipitated during the reaction can be isolated by filtration, washed with CH₂Cl₂ (10 mL), dried and weighed (Yields: 80-96%).

Sodium palmitate precipitates after the addition of diethyl ether (20 mL) to the reaction mixture.

In the case of the saponification of the Fmoc-protected amino acids {Fmoc-Asp (O-*t*-Bu)-OH and Fmoc-Glu(O-*t*-Bu)-OH}, 9-methylenefluorene, derived from the Fmoc group, was extracted first with diethyl ether (2x20 mL). The amino acid was isolated by freeze drying of the aqueous solution of its sodium salt, followed by preparative chromatographic separation of the amino acids, using a solvent mixture of 1-propanol, acetic acid and water in the ratio 12:3:5 by volume. Two additional equivalents of NaOH were required for hydrolysis, due to the COOH group and Fmoc deprotection. Increased equivalents of NaOH were also required with very crowded or unreactive compounds (**2**, **10**, **12**, **15**, and **16**). *N*-Tosyl indole (**16**) gave sodium tosylate and indole. The alkaline aqueous phase was first neutralised with dilute HCl and then extracted with ether.

General procedure for saponification using classical conditions. To a solution of the ester (1 mmol) in CH₃OH (7 mL) and H₂O (2 mL), a methanolic solution of 3 N NaOH (1 mL, 3 mmol) was added with stirring; the final concentration of the alkali being 0.3 N and the solvent mixture CH₃OH/H₂O (8:2, v/v, 10 mL). The progress of the reaction was monitored by TLC. The mixture was stirred until the ester was consumed (TLC) (Table 1), and then the solvents were removed under vacuum. The residue was diluted with water (10 mL), and subsequently extracted with ethyl acetate or diethyl ether (2x20 mL) to isolate the water-insoluble alcohol and/or to remove unreacted ester. The aqueous phase was cooled, acidified to pH ~2 with dilute HCl and extracted with AcOEt (2x20 mL). The combined organic layers were dried (Na₂SO₄) and the solvent removed to afford the acid. Yields for the resulting acids or alcohols were not determined as our interest was to measure and compare the completion times of the reactions (by TLC) of the two methodologies.

***t*-Butyl esters syntheses.** The esters **1-3** had been prepared by reaction of *tert*-butanol (2-4 mmol) in dry dichloromethane (DCM) (20 mL) and the appropriate acid chloride (2 mmol). To the stirring mixture was added triethylamine (5 mmol) in dry dichloromethane (5 mL) at 0 °C under argon. After addition was complete, the mixture was stirred for an additional 1-2 h at room temperature, then refluxed until completion (approximately 1 h). At the end of the reaction (as determined by TLC), the reaction mixture was cooled and evaporated to dryness. The residue was diluted with CH₂Cl₂ and extracted with H₂O, 5% NaHCO₃ and H₂O. The organic layer was dried over Na₂SO₄, concentrated *in vacuo*, and purified by column chromatography (CH₂Cl₂/hexane) on silica to afford the desired products (overall yields 74-80%). Their identities were confirmed by ¹H NMR spectroscopy.

Diphenylmethyl palmitate synthesis (4). The ester **4** has been prepared as above, from diphenyl methanol and palmitoyl chloride (Yield 75%).

***t*-Butyl *N*-methacryloyl-L-prolinate synthesis (8).** To a solution of the methacrylic acid (2 mmol) in dry DCM (5 mL), *t*-butyl-L-prolinate (2 mmol), *N,N'*-Dicyclohexylcarbodiimide (DCC) (2 mmol) and Et₃N (5 mmol) in DCM (2 mL) was added. The mixture was allowed to stir at 0 °C for 5 minutes. Stirring was continued overnight at rt until completion of the reaction (by TLC). After completion, it was concentrated to dryness. The residue was diluted with AcOEt (50 mL) and extracted with H₂O (20 mL), then with a solution of NaHCO₃ (2x15 mL), H₂O, and finally with a solution of KHSO₄. The organic layer was dried over MgSO₄ and the crude product was purified by column chromatography (CH₂Cl₂/hexane) on silica gel. Yield: 64%.

Syntheses of tosylates and *N*-tosylamines (13, 14, 17, 18).³⁸ To a solution of the suitable alcohol, phenol or amine (2 mmol) in dry DCM (10 mL), and cooled to 0 °C, was added, portion-wise and drop-wise, 4-dimethylaminopyridine (0.4 mmol), *p*-toluenesulfonyl chloride (2.4 mmol) and triethylamine (3.00 mmol). The reaction mixture was stirred at 0 °C until TLC showed complete consumption of starting material. The resulting

suspension was diluted with diethyl ether (25 mL), stirred for a further 30 min, and the precipitate removed by filtration. The solution was then washed sequentially with water (40 mL), 10% NaHCO₃ (2x25 mL) and a saturated aqueous NaCl solution (10 mL). The combined organic layers were dried over MgSO₄, filtered, concentrated *in vacuo*, and purified by column chromatography (CH₂Cl₂/hexane).

Syntheses of *N*-tosyl pyrrole and *N*-tosyl indole (15, 16).³⁹ A mixture of the indole or the pyrrole (1 mmol), *p*-toluenesulfonyl chloride (2 mmol), K₂CO₃ (4 mmol) and toluene (15 mL) was heated at reflux with stirring. After 15 h, the resulting suspension was filtered hot and the solution was concentrated under reduced pressure. The residue was diluted with diethyl ether (15 mL) and triturated with hexane. The precipitate was removed by filtration and crystallised from EtOH-hexane to yield 85% and 75% of products **15** and **16**, respectively.

***t*-Butyl *p*-nitrobenzoate (1).** White solid (80%, 0.36 g), mp 107-108 °C; ¹H NMR (CDCl₃, 500 MHz): δ_H 1.62 (s, 9H, *t*-Bu), 8.14 (d, 2H, ³J_{HH} 8.5 Hz, CH aromatic), 8.26 (d, 2H, ³J_{HH} 8.5 Hz, CH aromatic); Anal. Calcd. for C₁₁H₁₃NO₄: C, 59.19; H, 5.87; N, 6.27; found: C, 59.03; H, 5.91; N, 6.17%.

Di-*t*-butyl 2-methylmalonate (2). White viscous liquid (80%, 0.37 g); ¹H NMR (CDCl₃, 500 MHz): δ_H 1.32 (d, 3H, CHCH₃, ³J_{HH} 7 Hz), 1.46 (s, 18H, 2x-*t*-Bu), 3.22 (q, 1H, CHCH₃, ³J_{HH} 7.0 Hz); Anal. Calcd. for C₁₂H₂₂O₄: C, 62.58; H, 9.63; found: C, 62.30; H, 9.82%.

***t*-Butyl palmitate (3).** White viscous liquid (74%, 0.46 g); ¹H NMR (CDCl₃, 500 MHz): δ_H 0.88 (t, 3H, CH₃, ³J_{HH} 7.0 Hz), 1.22-1.35 (m, 24H, {CH₂}₁₂), 1.44 (s, 9H), 1.54-1.60 (m, 2H, CH₂CH₂COO-*t*-Bu), 2.19 (t, 2H, CH₂CH₂COO-*t*-Bu *J* 7.5 Hz); Anal. Calcd. for C₂₀H₄₀O₂: C, 76.86; H, 12.90; found: C, 76.91; H, 12.78%.

Diphenylmethyl palmitate (4). White viscous liquid (75%, 0.64 g). ¹H NMR (CDCl₃, 500 MHz): δ_H 0.88 (t, 3H, CH₃, ³J_{HH} 7.0 Hz), 1.20-1.35 (m, 24H, {CH₂}₁₂), 1.62-1.69 (m, 2H, CH₂CH₂COOAr), 2.42 (t, 2H, CH₂CH₂COOAr, ³J_{HH} 7.5 Hz), 7.26-7.34 (m, 10H, CH aromatic); Anal. Calcd. for C₂₉H₄₂O₂: C, 82.41; H, 10.02; found: C, 82.28; H, 9.98%.

***t*-Butyl *N*-methacryloyl-L-prolinate (8).** White viscous liquid (64%, 0.30 g); ¹H NMR (CDCl₃, 500 MHz): δ_H 1.46 (s, 9H, *t*-Bu), 1.80-2.20 (m, 6H), 2.22-2.25 (m, 1H), 3.57-3.64 (m, 2H), 4.38 (m, 1H), 5.05-5.27 {2H for two rotamers, each one pair of singlets (*trans* ~67% and *cis* ~33%), vinyl moiety (=CH₂)}; Anal. Calcd. for C₁₃H₂₁NO₃: C, 65.25; H, 8.84; N, 5.85; found: C, 65.13; H, 8.90; N, 5.78%.

Phenyl tosylate (13). White solid (89%, 0.44 g), mp 93-94 °C; ¹H NMR (CDCl₃, 500 MHz): δ_H 2.45 (s, 3H, CH₃), 6.98 (d, 2H, CH aromatic, ³J_{HH} 8.0 Hz), 7.24-7.31 (m, 5H, CH aromatic), 7.70 (d, 2H, CH aromatic, ³J_{HH} 8.0 Hz); Anal. Calcd. for C₁₃H₁₂O₃S: C, 62.88; H, 4.87; found: C, 63.05; H, 4.72%.

***N*-tosyl-indole (16).** Brown solid (85%, 0.46 g), mp 81-83 °C (EtOH/hexane); ¹H NMR (CDCl₃, 500 MHz): δ_H 2.33 (s, 3H, CH₃), 6.65 (d, 1H, CH aromatic, ³J_{HH} 3.5 Hz), 7.20-7.32 (m, 4H, CH aromatic), 7.52 (d, 1H, CH aromatic, ³J_{HH} 8.0 Hz), 7.56 (d, 1H, CH aromatic, ³J_{HH} 3.5 Hz), 7.76 (d, 2H, ³J_{HH} 8.0 Hz), 7.99 (d, 2H, ³J_{HH} 8.5 Hz); Anal. Calcd. for C₁₅H₁₃NO₂S: C, 66.40; H, 4.83; N, 5.16; found: C, 66.26; H, 4.89; N, 5.10%.

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Supplementary Material

Chiral HPLC analysis for hydrolysis of esters of L-amino acids and copies of ^1H NMR spectra of esters and corresponding hydrolysis products are provided in the online Supplementary Material file associated with this manuscript.

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