Eco-Friendly Bio-Based Solvents for the Acetylation of the Amino Group of Amino Acids

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Nature-derived products, like juices and peel extracts of fruits and vegetables, have emerged in recent years as interesting and sustainable alternatives to traditional solvents in several synthetic applications. Herein, we present a green and fast method for the *N*-acetylation of amino acids, using several bio-based solvents (vinegar, tomato/kiwi/apple peel extracts, lemon juice, *etc.*). The high reactivity of the amino group is often a limitation in synthetic processes, making its protection a necessary step to achieve pure products and limit side reactions. Therefore, versatile, time-efficient procedures, minimal purification efforts, and good yields are desirable features for these transformations. Our new method meets all these criteria, offering a valuable and eco-friendly alternative to traditional approaches. In detail, we managed to obtain comparable yields to established setups, while improving safety and reducing the environmental impact of the overall process. Most notably, the milder conditions made it possible to avoid the use of running water (saving about 250 L/reaction) and electric-powered cooling devices.

Keywords: Acetylation • Amino acids • Biowaste • Natural solvent • Protecting groups

Introduction

The development of green processes has become in the last years one of the main goals of the pharmaceutical sector.[1–8] The need to reduce the human impact on the environment has highlighted the importance of the application of green chemistry principles in the assessment of the sustainability of synthetic pathways.[9–11] One of the key pillars of this approach is the elimination/reduction of the use of solvents or the replacement of hazardous ones with environmentally benign alternatives. Solvents constitute 80-90% of the amount of material used in the pharmaceutical industry for a typical synthetic process. Furthermore, their handling consumes about 60% of the overall energy and accounts for 50% of the gas emissions. Hence, considering the volume of the pharmaceutical market and the environmental impact of industrial processes, measures should be urgently taken to identify safer and more sustainable options.[11,12] The recent increase in environmental awareness has also led to the realization that food waste can be a valuable resource, with potential applications in the industrial supply chains.[1–8] In detail, fruit- or plant-derived products can be employed for a variety of purposes, including the formulation of biofilms and matrices, the modification of the physicochemical properties of materials, and the development of nutraceuticals in the food industry.[13–16] Furthermore, an emerging possibility is the use of peels and juices from fruits and vegetables as efficient solvents and biocatalysts.[17–21]

In our group, we focused our attention on the development of a green process for the acetylation of amino acids. This reaction is a key step in several synthetic pathways used in the production of bioactive compounds, chelating agents, coordination polymers, and ionic liquids.[22–32] The presence of highly reactive functional groups, such as amines, requires the use of protective moieties, especially in multi-step organic synthesis. In detail, the protection of amino acids is of critical importance in many areas of medicinal chemistry and chemical biology.[33,34] Among the available options, the acetyl group can be particularly convenient because it is small, offers a good protection against a variety of side reactions, and is readily cleavable under mild conditions. Moreover, it is generally considered a low-impact protective agent.[35] In the literature, several methods have been reported for the acetylation of amino groups. For amino acids, the most frequently applied procedure involves the use of acetic anhydride in methanol. Acetic anhydride is usually preferred to acetyl chloride as the acetylating agent because it is easily available, cheap, and less prone to side reactions, due to its higher stability. Despite simple alcohols (methanol and ethanol) are environmentally preferable to more elaborate solvents (*e.g.*, tetrahydrofuran, cyclohexanone),[36] methanol is highly poisonous for humans, potentially harmful for the aquatic ecosystem, and damaging to plants.[37–39] Hence, the selection of safer solvents should be prioritized. Herein, we report a simple and sustainable method for the synthesis of *N*-acetylated amino acids using nature-derived solutions, such as

vinegar, peel extracts, and fruit juices (Figure 1). The versatility of our approach was verified using several amino acids, belonging to different chemical classes. Considering the relevance of this reaction, the low-to-non-existent impact of these bio-based solvents, and the efficiency of the proposed method, we expect that this work will contribute to the implementation of more responsible practices, even at the industrial level, and promote a gradual transition towards a circular economy model.

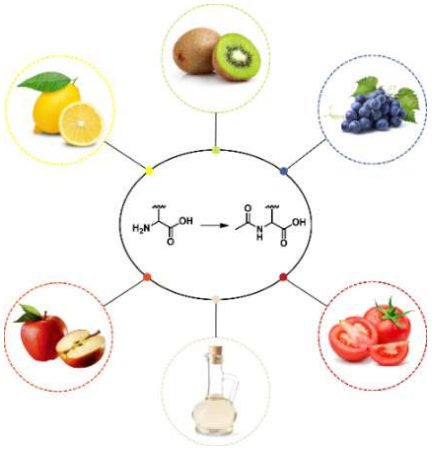
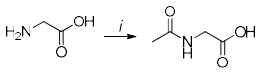


Figure 1. Graphical representation of the bio-based solvents and their natural sources, employed for the acetylation of the amino group of amino acids.[i]

Results and Discussion

The acetylation of amino acids, and particularly glycine, is a common reaction in several synthetic procedures, especially in the medicinal chemistry field. Traditional conditions require the use of methanol and acetic anhydride at reflux for 5-6 h.[27,40–42] In our efforts to optimize the reaction and reduce its impact on human health and on the environment, we tested the effect of several bio-based solvents, obtained directly from natural sources or organic waste. In detail, we based our selection on their acidic properties (pH < 5), considering that it is well-known that, in the traditional setup, acetic anhydride reacts with methanol producing methyl acetate and acetic acid. Therefore, after assessing the pH of a number of potential samples, we chose (I) grape and alcohol vinegar, (II) lemon, grapefruit, kiwi, tomato, and apple peel extracts, and (III) lemon and apple juices as our test media. We started our experimental evaluations with glycine because it is the most common amino acid substrate for this kind of reaction, according to Reaxys®. In a typical setup, glycine was suspended in the test medium, acetic anhydride was added dropwise, and the mixture was stirred for 20 min at room temperature (Scheme 1). Pure *N*-acetyl glycine was isolated as a white solid upon filtration, without the need of further purification.



Scheme 1. Reagents and conditions: *i)* Ac_2O (3.5 equiv.), test medium, 20 min., RT.

A blank experiment, accomplished by employing distilled water as the solvent, resulted in a poor conversion (yield < 20%). The yields obtained with the various test media are shown in Table 1. The most efficient bio-based solvents allowed the isolation of the product in good yields, reproducing the efficiency of the traditional reaction. Most notably, all of them were superior to distilled water. This observation confirmed the importance of an acidic environment for the success of the acetylation. Hence, the ability of the selected media to promote the reaction was ascribed to the presence of organic acids (citric, linolic, acetic, tartaric, malic, oxalic, succinic, *etc.*) in all the extracts. However, the pH was not the only factor influencing the transformation, as confirmed by the lower yield achieved with lemon juice with respect to grape and alcohol vinegar. Interestingly, a control experiment, accomplished employing distilled water acidified to the same pH of vinegar (pH= 2.30) with 3 M HCl, resulted in a significant reduction of the yield. Hence, we concluded that the acetic acid contained in vinegar acted as a better mediator of the *N*-acetylation reaction. This observation was also corroborated by the literature: for example, Sharley and Williams reported the use of catalytic amounts of acetic acid to promote the *N*-acetylation of amines in acetate esters.[43] As a proof of concept, a second control experiment was set up employing distilled water acidified to pH = 2.30 with acetic acid. In these conditions, we obtained a comparable yield to that observed using vinegar as the solvent. Most notably, the replacement of acetic acid, a flammable and corrosive liquid, may be preferable to improve process safety and facilitate chemical handling, especially in large-scale productions.

The performances of the various bio-based solvents as a function of the pH are shown in Table 1 and plotted in a scatter chart in Figure 2. The importance of the acidic pH is evidenced by its inverse correlation with the yield; at the same time, it is also clear that not all acids perform comparably in catalyzing the reaction.

Table 1. Yields for the acetylation of glycine in the selected aqueous media, compared to the traditional reaction (first line).

Medium	Yield ± SD (%)*	pH
MeOH**	70 ± 5.6**	-
Distilled water	20 ± 4.2	6.72
Grape vinegar	70 ± 6.4	2.37
Alcohol vinegar	70 ± 5.7	2.34
Lemon juice	58 ± 3.5	2.30
Grape peel	48 ± 7.7	3.90
Apple Juice	42 ± 2.6	3.86
Kiwi peel	41 ± 6.7	3.65
Tomato peel	39 ± 3.4	4.57
Lemon peel	36 ± 8.3	3.89
Apple peel	33 ± 4.7	3.96

* The yields are calculated as the mean of three replicates.
** Traditional reaction conditions: MeOH, 6 h, 60 °C.

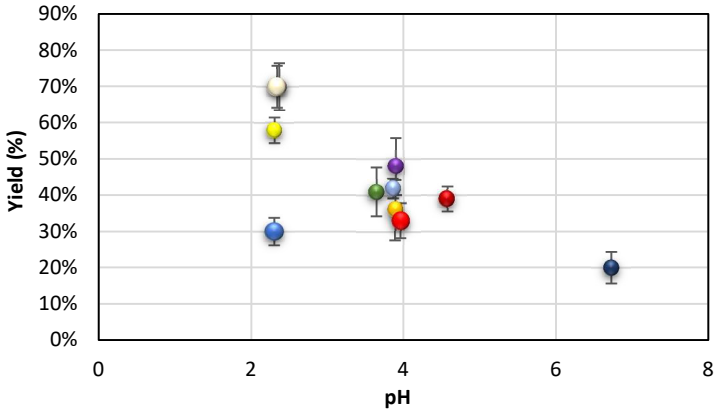


Figure 2. Scatter plot for the yields of the *N*-acetylation of glycine *vs* the pH of the selected bio-based solvents. The highest yields were observed for pH values around 2. Grape vinegar; Alcohol vinegar; Lemon juice; Grape peel; Apple juice; Kiwi peel; Tomato peel; Lemon peel; Apple peel; Distilled water, pH = 2.3; Distilled water.

The synthesis of *N*-acetyl glycine in grape vinegar was also performed increasing the time up to 1 h, or heating to 60 °C for 20 min, but no improvement in the yield was observed. Therefore, the best reaction conditions (using vinegar as the solvent) were applied for the acetylation of other amino acids to verify the versatility of the process. Alanine, serine, phenylalanine, glutamic acid, and arginine were each selected as representatives of all the amino acid classes (non-polar, polar, aromatic, negatively and positively charged, respectively). Moreover, lysine was chosen to investigate the selectivity of the reaction. The synthetic procedure remained the same for all amino acids, with the only exception of glutamic acid, which was previously heated at reflux for 10 min in vinegar to increase its low solubility in aqueous media. After this preliminary step, the reaction was continued at room temperature for 20 min. Concerning the workup, pure serine and phenylalanine were isolated as white solids upon filtration, whereas alanine, glutamic acid, arginine, and lysine were obtained as pure products by the evaporation *in vacuo* of the reaction mixture (Table 2). Interestingly, when lysine was used as the substrate, only the α-amino group was successfully acetylated, demonstrating the selectivity of the process.

Table 2. Yields for the *N*-acetylation of various amino acids in grape vinegar.

Reagent	Yield (%)
Alanine	90%
Serine	60%
Phenylalanine	50%
Glutamic acid	95%
Arginine	72%
Lysine	70%

Furthermore, we observed that vinegar could be recovered upon filtration of the reaction mixture and recycled to perform further

acetylation steps on new batches of the same substrate, without loss of efficiency. Interestingly, we experimentally detected increased yields in the reactions with the recovered media, probably due to the carryover of residual acetylated product and/or reagents upon filtration.

This new, sustainable method led to the obtaining of the desired *N*-acetylated amino acid derivatives in good-to-excellent yields, by using low-impact, natural solvents. Overall, the traditional reaction was optimized in terms of (I) safety and environmental friendliness of the solvents, (II) time, and (III) temperature, while maintaining comparable yields. The selected media were either derived from biowaste, thus promoting the recycling of the resources and a circular economy approach, or from very cheap and easily accessible natural sources. The reaction times were considerably shortened (from 5 h to only 20 min), with comparable efficiency, curbing the overall energetic burden of the process. Moreover, the use of room temperature instead of harsher reflux conditions for a prolonged time made it possible to avoid the use of running water (saving approximately 250 L/reaction) or electric-powered cooling devices, thus sensibly increasing the sustainability of the process, especially in the context of the current climate and energetic crisis.

Conclusions

In this work, we developed a novel method for the sustainable production of *N*-acetyl amino acids. We demonstrated that non-toxic, cheap, non-polluting, easy-to-obtain natural juices and food waste can act as efficient bio-based solvents for the protection of different amino acids. The main advantages of our process are the simple workup, mild reaction conditions, short times, and excellent yields. In detail, the green process offered a comparable efficiency to that of the traditional method and improved the reaction conditions, reducing the time and removing the heating step. Finally, we hope that this work may lay the foundations for the optimization of seemingly routine and simple chemical reactions with a greener perspective.

Experimental Section

All starting reagents and solvents were purchased from commercial suppliers (Merck KGaA, Darmstadt, Germany; FluoroChem, Hadfield, UK) and used as received. The pH of the bio-based solvents was measured with a Hanna HI 207 pH meter (Hanna Instruments Italia Srl, Baranzate, Italy). Centrifugation steps were carried out on an MPW-56 lab centrifuge (MPW Med. Instruments, Warsaw, Poland), using standard test tubes. The course of the reactions was followed by thin-layer chromatography (TLC), using aluminum-backed silica gel 60 plates (0.2 mm; Merck KGaA). The visualization was aided by an acidic ninhydrin solution as a staining reagent. The final products were retrieved by filtration using Whatman® filter paper (Merck KGaA) or obtained by evaporation under reduced pressure of the reaction mixtures. The identity of the compounds was verified by means of ^{1}H NMR. Spectra were acquired at ambient temperature on a Varian Oxford instrument (Varian, Palo Alto, CA, USA), operating at 300 MHz, and compared to literature data. Chemical shifts are expressed in ppm (δ), and *J*-couplings are given in Hertz. The yields of the reactions are reported in Table 1 and Table 2. All further details are reported in the Supporting Information.

Preparation of juices and extracts

Juices were obtained by squeezing the fruits, followed by centrifugation and filtration on a Büchner funnel. The peels were extracted by boiling approximately 30 g of starting material in 25 mL of distilled water for 30 min and leaving to infuse for 3 h. The resulting suspension was filtered by suction to afford the desired extracts (see Supporting Information). Grape and alcohol vinegar (6% acidity) were acquired from a local grocery store and used as such without any purification.

Synthesis of *N*-Acetyl amino acids

Method A (green process)

N-acetyl glycine. Acetic anhydride (9.31 mmol, 3.5 equiv.) was added to a solution of 2-aminoacetic acid (2.66 mmol, 1 equiv.) in the desired juice or extract (1 mL), and the mixture was stirred for 20 min at room temperature. Then, the resulting precipitate was collected by filtration to afford the desired pure product as a white solid, without the need of further purification. ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 8.14 (s, 1H, NH), 3.70 (d, *J* = 5.9 Hz, 2H, CH_2), 1.82 (s, 3H, CH_3).

N-acetyl alanine. Method A. Solvent: grape vinegar. The desired product was obtained as a white solid by the evaporation under reduced pressure of the reaction mixture. ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 8.11 (d, *J* = 6.8 Hz, 1H, NH), 4.13 (q, *J* = 7.3 Hz, 1H, CH), 1.80 (s, 3H, CO$\underline{CH_3}$), 1.22 (d, *J* = 7.3 Hz, 3H, CH$\underline{CH_3}$).

N-acetyl serine. Method A. Solvent: grape vinegar. The desired product was obtained as a white solid by the evaporation under reduced pressure of the reaction mixture. ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 7.99 (d, *J* = 7.8 Hz, 1H, NH), 4.24 (dt, *J* = 9.3, 4.9 Hz, 1H, CH), 3.69 – 3.56 (m, 2H, CH_2), 1.86 (s, 3H, CH_3).

N-acetyl phenylalanine. Method A. Solvent: grape vinegar. Aspect: white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 8.15 (d, *J* = 8.1 Hz, 1H, NH), 7.41 – 6.87 (m, 5H, aromatic H), 4.42 – 4.34 (m, 1H, CH), 3.02

(dd, *J* = 13.8, 4.9 Hz, 1H, CH_2), 2.81 (dd, *J* = 13.8, 9.5 Hz, 1H, CH_2), 1.76 (s, 3H, CH_3).

N-acetyl glutamic acid. Method A. Solvent: grape vinegar. The suspension of glutamic acid in vinegar was heated at reflux for 10 min to allow the solubilization of the amino acid in the aqueous medium; then, acetic anhydride was added, and the reaction was stirred at room temperature for 20 min. The desired product was obtained as a white solid by the evaporation *in vacuo* of the mixture. ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 8.08 (d, *J* = 7.7 Hz, 1H, NH), 4.16 (q, *J* = 8.1 Hz, 1H, CH), 2.25 (t, *J* = 7.1 Hz, 2H, CO*CH*$_2$), 1.87 – 1.57 (m, 5H, CH_2 and CH_3).

N-acetyl arginine. Method A. Solvent: grape vinegar. The desired product was obtained as a white solid by the evaporation under reduced pressure of the reaction mixture. ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 9.19 (d, *J* = 3.6, 1H, NH), 7.67 – 7.52 (m, 3H, *NH*$_2$C*NH*), 3.93 (q, *J* = 7.0, 6.4 Hz, 1H, CH), 3.06 – 2.96 (m, 2H, NH*CH*$_2$), 1.80 (s, 3H, CH_3), 1.73 – 1.32 (m, 4H, CH_2).

N-acetyl lysine hydrochloride. Method A. Solvent: grape vinegar. Starting reagent: lysine hydrochloride. The desired product was obtained as a white solid by the evaporation under reduced pressure of the reaction mixture. ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) δ 8.13 (d, *J* = 7.5 Hz, 1H, NH), 7.87 (br s, 3H, NH_3^+), 4.12 (q, *J* = 8.0 Hz, 1H, CH), 2.73 (s, 2H, *CH*$_2$$NH_3^+$), 1.83 (s, 3H, CH_3), 1.71 – 1.44 (m, 4H, CH_2), 1.41 – 1.21 (m, 2H, CH_2).

Method B (traditional procedure)

N-acetyl glycine. Acetic anhydride (9.31 mmol, 3.5 equiv.) was added to a solution of 2-aminoacetic acid (2.66 mmol, 1 equiv.) in MeOH (1 mL), and the mixture was refluxed for 6 h. Then, the volatiles were evaporated *in vacuo*, and the residue was washed with MeOH to afford the desired product as a white solid. [27,40–42]

Supplementary Material

Supporting information for this article is available on the website

Author Contribution Statement

Giulia Cazzaniga, Matteo Mori: Conceptualization; Fiorella Meneghetti, Arianna Gelain, Stefania Villa: Funding acquisition; Giulia Cazzaniga, Matteo Mori, Andrea Tresoldi: Investigation; Giulia Cazzaniga, Matteo Mori: Writing - original draft; Giulia Cazzaniga, Matteo Mori, Fiorella Meneghetti, Arianna Gelain, Stefania Villa: Writing - review & editing.

Conflicts of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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