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Lipase Catalyzed Solvent-Free Amidation of Phenolic Acids

Parshant Kaushik^a, Najam Akhtar Shakil^a, Jitendra Kumar^a & Braj Bhushan Singh^a

^a Division of Agricultural Chemicals, Indian Agricultural Research Institute, New Delhi, India

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LIPASE CATALYZED SOLVENT-FREE AMIDATION OF PHENOLIC ACIDS

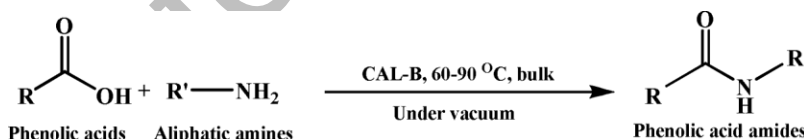
Parshant Kaushik¹, Najam Akhtar Shakil¹, Jitendra Kumar¹, Braj Bhushan Singh¹

¹Division of Agricultural Chemicals, Indian Agricultural Research Institute, New Delhi, India

Corresponding author- Najam Akhtar Shakil, Division of Agricultural Chemicals, Indian Agricultural Research Institute, New Delhi 110012. India E-mail: iamshakil@gmail.com

Abstract

A series of N-alkyl substituted amides, based on various phenolic acids, have been synthesized by the condensation of equimolar amounts of phenolic acids with different alkyl amines in presence of *Candida antarctica* lipase at 60-90 °C in 16-20 h. The reactions were carried out in a non - solvent system without the use of any activating agents. All the products were obtained in appreciable amounts and the yields for different compounds varied between 75.6 - 83.5%. The synthesized compounds were characterized using spectroscopy techniques namely IR and NMR (¹H and ¹³C).



KEYWORDS: Phenolic acids, N-substituted amides, *Candida antarctica* lipase, Non-solvent system

INTRODUCTION

Cinnamic acids and their synthetic esters, amides and glycosides exhibit a wide range of activities, including the anti-oxidative effect on low density lipoprotein (LDL),^[1] the

peroxyl radical scavenging effect,^[2] anti-inflammatory^[3] and anti-mutagenic effect.^[4] The cholesterol lowering effect of several hydroxylated cinnamic acid derivatives of amino acids has been evaluated in mice fed with high cholesterol diets.^[5] The presence of double bond in hydroxylated cinnamide derivatives decreases the cholesterol-lowering activities and the number of free phenolic hydroxyl groups greatly affects the biological activity. Amides of phenolic acids having hydrophobic side chains exhibit potent cholesterol lowering effect.^[6] The amides of cinnamic and hydroxycinnamic acids with aliphatic monoamines have been synthesized and their radical scavenging activity against DPPH tests have been reported.^[7,8] Substituted amides and amines are also important because of the presence of these functional groups in many compounds having both medicinal as well as pesticidal activity. They are reported to have antibacterial, antifungal, antiviral, insecticidal, nematocidal and herbicidal properties.^[9-21] Synthesis of these compounds have mainly been achieved by classical chemical reactions, which generally involve the generation of a reactive carboxy derivative, either an acid chloride or anhydride, followed by aminolysis with amine. Also, the conversion of esters to amides has some limitations as the commonly used reagents, that is, sodium methoxide, sodium hydride, sodium metal or butyl lithium often interfere with other functional groups present in the reacting species. Among the many significant advances in organic chemistry, attempts for environmentally benign processes in organic synthesis have highlighted the importance of enzyme catalyzed reactions, particularly for large-scale industrial applications.^[22] Enzyme-catalyzed organic reactions have provided a great impetus to organic synthesis during the last two decades. Enzymes, especially lipases are known for their low cost and great tolerance towards their substrates. Environmentally benign character of the

enzymatic processes is desirable for large scale industrial applications. Even though some enzyme catalyzed reactions for the synthesis of amides were reported, most of them involved the use of activating agents or solvents and the bioactivity of these synthesized compounds was hardly studied.^[23-31]

Considering these facts, we got interested in search of new phenolic acids analogues. We envisaged developing a one-pot biocatalytic amidation procedure by using lipase as catalyst. In this report, we have carried out *C. antarctica* lipase (CAL-B) catalysed amidation of phenolic acids by different aliphatic amines in bulk (without solvent) at 60–90 °C.

RESULTS AND DISCUSSION

The condensation of equimolar amount of different phenolic acids namely salicylic acid (**1**), 3-hydroxy cinnamic acid (**2**), p-coumaric acid (**3**), caffeic acid (**4**), ferulic acid (**5**), o-coumaric acid (**6**) and cinnamic acid (**7**) with amines *viz* propyl amine (**8a**), hexyl amine (**8b**), heptyl amine (**8c**), undecyl amine (**8d**), hexadecyl amine (**8e**) and octadecyl amine (**8f**), catalyzed by *Candida antarctica* lipase (CAL-B) in a non solvent system at 60–90 °C in 16–20 h resulted in the formation of N-propyl-salicylamide (**9a**), N-hexyl-salicylamide (**9b**), N-heptyl-salicylamide (**9c**), N-undecyl-salicylamide (**9d**), N-hexadecyl-salicylamide (**9e**), N-octadecyl-salicylamide (**9f**), N-propyl-3-hydroxycinnamamide (**10a**), N-hexyl-3-hydroxycinnamamide (**10b**), N-heptyl-3-hydroxycinnamamide (**10c**), N-undecyl-3-hydroxycinnamamide (**10d**), N-hexadecyl-3-hydroxycinnamamide (**10e**), N-octadecyl-3-hydroxycinnamamide (**10f**), N-propyl-4-

hydroxycinnamamide (**11a**), N-hexyl-4-hydroxycinnamamide (**11b**), N-heptyl-4-hydroxycinnamamide (**11c**), N-undecyl-4-hydroxycinnamamide (**11d**), N-hexadecyl-4-hydroxycinnamamide (**11e**), N-octadecyl-4-hydroxycinnamamide (**11f**), N-propyl-3,4-dihydroxycinnamamide (**12a**), N-hexyl-3,4-dihydroxycinnamamide (**12b**), N-heptyl-3,4-dihydroxycinnamamide (**12c**), N-undecyl-3,4-dihydroxycinnamamide (**12d**), N-hexadecyl-3,4-dihydroxycinnamamide (**12e**), N-octadecyl-3,4-dihydroxycinnamamide (**12f**), N-propyl-4-hydroxy-3-methoxycinnamamide (**13a**), N-hexyl-4-hydroxy-3-methoxycinnamamide (**13b**), N-heptyl-4-hydroxy-3-methoxycinnamamide (**13c**), N-undecyl-4-hydroxy-3-methoxycinnamamide (**13d**), N-hexadecyl-4-hydroxy-3-methoxycinnamamide (**13e**), N-octadecyl-4-hydroxy-3-methoxycinnamamide (**13f**), N-propyl-2-hydroxycinnamamide (**14a**), N-hexyl-2-hydroxycinnamamide (**14b**), N-heptyl-2-hydroxycinnamamide (**14c**), N-undecyl-2-hydroxycinnamamide (**14d**), N-hexadecyl-2-hydroxycinnamamide (**14e**), N-octadecyl-2-hydroxycinnamamide (**14f**), N-propyl-cinnamamide (**15a**), N-hexyl-cinnamamide (**15b**), N-heptyl-cinnamamide (**15c**), N-undecyl-cinnamamide (**15d**), N-hexadecyl-cinnamamide (**15e**), N-octadecyl-cinnamamide (**15f**).

The feasibility of non-solvent system was investigated. The reactions with equimolar amounts of amines **8a-8f** and phenolic acids **1-7** were performed (Scheme 1). The reaction mixture was very viscous and the reaction temperature had to be raised up to 90 °C in order to achieve an efficient stirring in the system. There was a report in literature^[50] where the reaction temperature was maintained at 55 °C for the lipase catalyzed amidation. In that case, the reaction did not go to completion as some unreacted

acid and amine remained in the reaction mixture in salt form even after incubating the mixture for longer times. Such a situation did not arise in our study as the reaction temperature was kept between 60-90 °C under reduced pressure. The conversion of acids to amides was found to be 100% in 75.6-83.5% yields. The synthesized amides were fully characterized from their spectral data.

In IR spectra, Amide I band due to CO stretching appeared at approximately 1645 cm⁻¹, Amide II band due to N-H bending appeared at approximately 1560 cm⁻¹ and Amide III band due to C-N stretching appeared at approximately 1250 cm⁻¹, in all the products confirmed the condensation of carbonyl group with amino group. In ¹H NMR spectra, quartet at δ 3.15–3.3 for CONH-CH₂ and a singlet at δ 7.97-8.31 for the N-H proton were characteristic of all the synthesized amides. In ¹³C NMR, the peaks at δ 41.4 – 43.1 for CONHCH₂ and at δ 168–172.4 for CONH were prominent for all the compounds.

In addition to the above mentioned characteristics, bands at approximately 3425 cm⁻¹ (broad multiplet due to N-H stretching), 2932 cm⁻¹ (strong) and 783 cm⁻¹ (strong) were also present for all the test compounds in IR spectra. In ¹H NMR spectra, the signals in δ range 6.6–7.4 are of aromatic protons (Ar-H), a singlet at δ 4.80-5.29 for Ar-OH, a singlet at δ 3.7-3.8 for Ar-OCH₃ and doublets at δ 6.2-7.7 for vinylic protons were observed for the synthesized phenolic acid amides.

In ¹H NMR spectral analysis, the H-2' protons of all the propyl derivatives of phenolic acid amides appear as a multiplet in δ range 1.19-1.68, whereas the aliphatic protons of

the side chain of other amides appear in δ range 1.16-1.84. The ^1H and ^{13}C NMR of one representative amide from salicylic acid and phenolic acids is discussed here.

To the best of our knowledge, the results presented in this study demonstrate for the first time the phenolic acid amide synthesis in non solvent system by the direct lipase catalyzed reaction of amines with phenolic acids. The present enzymatic procedure offers some important advantages over the chemical one for the application in industrial processes.

EXPERIMENTAL

Laboratory grade reagents and solvents were procured from Qualigens. Different amines were procured from M/S Sigma Aldrich and used as received. *Candida antarctica* lipase, an immobilized enzyme, was a gift from Novozymes, Denmark. Thin Layer Chromatography (TLC) was performed on 200 μm thick aluminium sheets with silica gel as adsorbent. The solvent system used for developing the TLC plate was ethyl acetate: hexane, 2:8. Spots were visualized in UV/ iodine chamber. The Infra Red (IR) spectra were recorded on either a Perkin-Elmer 2000 Fourier Transform Infra Red (FT-IR). The ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker AC-300 Avance spectrophotometer at 400 and 100 MHz, respectively using Tetramethylsilane (TMS) as an internal standard. The chemical shift (δ) values are expressed in ppm and the coupling constants (J) values are in Hertz (Hz). The elemental analysis was done on a Eurovector Elemental analyzer 3000 using sulphanilamide as standard with linear calibration.

General Procedure For The Preparation Of N-Alkyl Substituted Phenolic Acid

Amides

A total of forty two phenolic acids based amides were synthesized by the biocatalytic condensation of different phenolic acids with amines in vacuum, out of which twenty, that is, **9a**, **10a**, **10b**, **10d**, **10e**, **10f**, **11c**, **11d**, **11e**, **12e**, **13d**, **13e**, **13f**, **14b**, **14c**, **14d**, **14e**, **14f**, **15d** and **15e**, were reported for the first time in literature (Sch. 1). For the same, equimolar amounts of different chain length amines and phenolic acids, along with *Candida antarctica* lipase enzyme (10% of the total amount of the reactants) were taken in a 250 mL, two necked round-bottom flask with a magnetic bar (to facilitate stirring) and was then heated in an oil bath at 60–90 °C. One neck of the round bottom flask was attached to a pump under vacuum and the other was punctured with a needle to regulate the pressure inside the round-bottom flask. The different reactions were allowed to proceed for 16–20 hours. The formation of products was confirmed by Thin Layer Chromatography (TLC) in ethyl acetate: hexane (2:8) solvent system. After completion, the reaction was quenched by adding dichloromethane (DCM), followed by filtration to remove the enzyme. The solvent DCM was then evaporated off in a rotary evaporator. The different phenolic acids based amides synthesized were purified by column chromatography to afford the pure amides in 75.6–83.5 % yield. Compounds **9b**, **9c**, **9d**, **9e**, **9f**, **10c**, **11a**, **11b**, **11f**, **12a**, **12b**, **12c**, **12d**, **12f**, **13a**, **13b**, **13c**, **14a**, **15a**, **15b**, **15c**, and **15f** were earlier reported in literature.^[32–49]

Spectral Analysis Of Individual Amides Selected Data: N-Propyl-Salicylamide (**9a**)

It was obtained as a reddish brown coloured viscous liquid, after purification by column chromatography by eluting with 2% ethyl acetate in hexane in 81.4% yield, R_f : 0.46 (ethyl acetate: hexane, 2:8). IR (Nujol) cm^{-1} : 1643 (CO stretching, amide I band), 1557 (N-H bending, amide II band), 1261 (C-N stretching, amide III band), 3403 (N-H stretching). ^1H NMR (400 MHz, DMSO): δ 0.93 (3H, t, $J=7.6$, H-3'), 1.59–1.68 (2H, m, H-2'), 2.81 (2H, t, $J=7.6$, H-1'), 6.71 (1H, d, $J=8.4$, H-3''), 7.20–7.22 (2H, dd, $J=8.8$ & 2.1 and $J=8.4$ & 2.1 each, H-4'' & H-5''), 7.74 (1H, d, $J=7.6$, H-6'') and 8.31 (1H, s, N-H). ^{13}C NMR (75.5 MHz, DMSO): δ 11.1 (C-3'), 24.5 (C-2'), 42.7 (C-1'), 116.5 (C-1''), 119.0 (C-3''), 119.3 (C-5''), 129.6 (C-6''), 131.7 (C-4''), 161.7 (C-2'') and 172.7 (C-1). Analyzed for molecular formula $\text{C}_{10}\text{H}_{13}\text{NO}_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 67.23; H, 7.26; N, 7.69.

Selected Data: N-Propyl-3-Hydroxycinnamamide (10a)

It was obtained as a dark brown coloured solid, after purification by column chromatography by eluting with 2% ethyl acetate in hexane in 81.2% yield, R_f : 0.47 (ethyl acetate: hexane, 2:8). IR (Nujol) cm^{-1} : 1650 (CO stretching, amide I band), 1572 (N-H bending, amide II band), 1243 (C-N stretching, amide III band), 3258 (N-H stretching). ^1H NMR (400 MHz, DMSO): δ 0.81 (3H, t, $J=6.8$, H-3'), 1.56–1.67 (2H, m, H-2'), 3.19 (2H, t, H-1'), 4.80 (1H, s, Ar-OH); 6.35 (1H, d, $J=15.6$, H-2), 6.68 (1H, s, H-2''), 6.75 (1H, dd, $J=7.6$ & 2.0, H-5''), 6.94 (1H, d, $J=8.0$, H-4''), 7.16 (1H, d, $J=7.6$, H-6''), 7.24 (1H, d, $J=15.6$, H-3) and 8.17 (1H, s, N-H). ^{13}C NMR (75.5 MHz, DMSO): δ 14.3 (C-3'), 23.5 (C-2'), 42.5 (C-1'), 114.2 (C-4''), 115.7 (C-2''), 118.7 (C-2), 119.1 (C-6''), 129.0 (C-5''), 136.0 (C-1''), 139.6 (C-3), 158.7 (C-3'') and 170.7 (C-1). Analyzed for

molecular formula $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.15; H, 7.42; N, 6.97.

Selected Data: N-Propyl-4-Hydroxycinnamamide (11a)^[36]

It was obtained as a light brown coloured solid, after purification by column chromatography by eluting with 2% ethyl acetate in hexane in 77.2% yield, R_f : 0.49 (ethyl acetate: hexane, 2:8). IR (Nujol) cm^{-1} : 1654 (CO stretching, amide I band), 1523 (N-H bending, amide II band), 1254 (C-N stretching, amide III band), 3422 (N-H stretching). 1H NMR (400 MHz, DMSO): δ 0.90 (3H, t, $J=8$, H-3'), 1.58–1.64 (2H, m, H-2'), 2.74 (2H, t, $J=7.6$, H-1'), 4.80 (1H, s, Ar-OH); 6.26 (1H, d, $J=16$, H-2), 6.78 (2H, d, $J=7.6$, H-3'' & H-5''), 7.33 (1H, d, $J=16$, H-3), 7.42 (2H, d, $J=8.8$, H-2'' & H-6'') and 8.17 (1H, s, N-H). ^{13}C NMR (75.5 MHz, DMSO): δ 14.2 (C-3'), 27.5 (C-2'), 43.5 (C-1'), 115.9 (C-3'' & C-5''), 119.1 (C-2), 127.6 (C-1''), 130.0 (C-6'' & C-2''), 143.1 (C-3), 159.9 (C-4'') and 169.7 (C-1). Analyzed for molecular formula $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.35; H, 7.27; N, 7.54.

Selected Data: N-Propyl-3,4-Dihydroxycinnamamide (12a)^[36]

It was obtained as a dark brown coloured viscous liquid, after purification by column chromatography by eluting with 2% ethyl acetate in hexane in 80.4% yield, R_f : 0.46 (ethyl acetate: hexane, 2:8). IR (Nujol) cm^{-1} : 1640 (CO stretching, amide I band), 1559 (N-H bending, amide II band), 1258 (C-N stretching, amide III band), 3423 (N-H stretching). 1H NMR (400 MHz, DMSO): δ 0.79 (3H, t, $J=7.6$, H-3'), 1.19–1.39 (2H, m, H-2'), 3.5 (2H, t, H-1'), 5.05 (1H, s, Ar-OH); 6.42 (1H, d, $J=14.8$, H-2), 6.52–6.54 (2H,

dd, $J=8.0$ & 2.0 and $J=8.0$ & 2.0 each, H-5'' & H-6''), 6.63 (1H, s, H-2''), 7.14 (1H, d, $J=14.8$, H-3) and 8.19 (1H, s, N-H). ^{13}C NMR (75.5 MHz, DMSO): δ 11.4 (C-3'), 27.4 (C-2'), 43.1 (C-1'), 113.5 (C-2''), 115.4 (C-5''), 121.0 (C-2), 123.7 (C-6''), 129.6 (C-1''), 139.6 (C-3), 144.8 (C-3''), 145.5 (C-4'') and 170.7 (C-1). Analyzed for molecular formula $\text{C}_{12}\text{H}_{15}\text{NO}_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.21; H, 6.74; N, 6.52.

Selected Data: N-Propyl-4-Hydroxy-3-Methoxycinnamamide (13a)^[43]

It was obtained as a dark red colored solid, after purification by column chromatography by eluting with 2% ethyl acetate in hexane in 83.6% yield, R_f : 0.49 (ethyl acetate: hexane, 2:8). IR (Nujol) cm^{-1} : 1645 (CO stretching, amide I band), 1571 (N-H bending, amide II band), 1254 (C-N stretching, amide III band), 3426 (N-H stretching). ^1H NMR (400 MHz, DMSO): δ 0.82 (3H, t, $J=7.2$, H-3'), 1.20–1.50 (2H, m, H-2'), 2.70 (2H, t, $J=7.4$, H-1'), 3.7 (3H, s, Ar-OCH₃) 5.04 (1H, s, Ar-OH); 6.29 (1H, d, $J=16$, H-2), 6.74 (1H, d, $J=8.0$, H-6''), 7.01 (1H, d, $J=7.6$, H-5'') 7.15 (1H, s, H-2''), 7.24 (1H, d, $J=16$, H-3) and 7.97 (1H, s, N-H). ^{13}C NMR (75.5 MHz, DMSO): δ 14.2 (C-3'), 27.2 (C-2'), 42.6 (C-1'), 56.0 (Ar-OCH₃), 111.1 (C-2''), 115.9 (C-5''), 119.4 (C-2), 122.9 (C-6''), 127.0 (C-1''), 139.5 (C-3), 144.7 (C-4''), 148.8 (C-3'') and 170.0 (C-1). Analyzed for molecular formula $\text{C}_{13}\text{H}_{17}\text{NO}_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.42; H, 7.26; N, 5.89.

Selected Data: N-Propyl-2-Hydroxycinnamamide (14a)^[45]

It was obtained as a dark brown coloured solid, after purification by column chromatography by eluting with 2% ethyl acetate in hexane in 78.7% yield, R_f : 0.49 (ethyl acetate: hexane, 2:8). IR (Nujol) cm^{-1} : 1646 (C O stretching, amide I band), 1567

(N-H bending, amide II band), 1223 (C-N stretching, amide III band), 3249 (N-H stretching). ¹H NMR (400 MHz, DMSO): δ 0.91 (3H, t, J=7.2, H-3'), 1.36–1.64 (2H, m, H-2'), 2.92 (2H, t, J=7.8, H-1'), 5.12 (1H, s, Ar-OH), 6.50 (1H, d, J=16, H-2), 6.74 (1H, d, J=7.6, H-3''), 6.88 (1H, dd, J=8.0 & 1.2, H-5''), 7.10–7.14 (2H, dd, J=8.4 & 1.6, H-4''), 7.46 (1H, d, J=7.6, H-6''), 7.74 (1H, d, J=16, H-3) and 8.21 (1H, s, N-H). ¹³C NMR (75.5 MHz, DMSO): δ 11.9 (C-3'), 26.3 (C-2'), 42.7 (C-1'), 116.6 (C-3''), 119.3 (C-2), 121.2 (C-5''), 122.4 (C-1''), 128.3 (C-6''), 129.1 (C-4''), 140.2 (C-3), 156.9 (C-2'') and 170.5 (C-1). Analyzed for molecular formula C₁₂H₁₅NO₂: C, 70.22; H, 7.37; N, 6.82. Found: C, 7.19; H, 7.33; N, 6.89.

Selected Data: N-Propyl-Cinnamamide (15a)^[46]

It was obtained as a dark brown colored viscous liquid, after purification by column chromatography by eluting with 2% ethyl acetate in hexane in 81.1% yield, R_f : 0.49 (ethyl acetate: hexane, 2:8). IR (Nujol) cm⁻¹: 1642 (CO stretching, amide I band), 1563 (N-H bending, amide II band), 1256 (C-N stretching, amide III band), 3448 (N-H stretching). ¹H NMR (400 MHz, DMSO): δ 0.88 (3H, t, J=7.2, H-3'), 1.37–1.65 (2H, m, H-2'), 2.75 (2H, t, J=7.6, H-1'), 6.53 (1H, d, J=16, H-2), 7.42 (1H, d, J=16, H-3), 7.3–7.5 (5H, m, Ar-H), 8.04 (1H, s, N-H). ¹³C NMR (75.5 MHz, DMSO): δ 13.9 (C-3'), 26.5 (C-2'), 41.9 (C-1'), 119.2 (C-2), 126.3 (C-4''), 127.5 (C-2'' & C-6''), 128.6 (C-3'' & C-5''), 135.3 (C-1''), 140.1 (C-3) and 171.4 (C-1). Analyzed for molecular formula C₁₂H₁₅NO: C, 76.16; H, 7.99; N, 7.40. Found: C, 76.23; H, 7.96; N, 7.45.

CONCLUSION

A novel, efficient and environmentally benign method for the synthesis of phenolic acid amides has been developed, which can be utilized for the synthesis of analogous compounds as this method avoids the use of activating agents for the conversion of acids to amides, which is otherwise not possible chemically.

SUPPORTING INFORMATION

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Scheme 1. Synthesis of phenolic acid amides

