

An Efficient Synthesis of N- Benzoyl Derivative of Amino Acids Using PEG-400 as A Green and Recyclable Catalyst

B K. Magare^{1*}, D W Shinde¹ and M. B. Ubale²

Associate Professor, Dept of Chemistry, Shivaji Arts, Commerce and Science College Kannad, Dist. Aurangabad, (M.S.) India¹

Professor, Dept of Chemistry, Vasantnao Naik Mahavidhyalaya, Aurangabad, (M. S.)India²

ABSTRACT : A simple, highly efficient synthesis of N-benzoyl derivatives of amino acids using polyethylene glycol (PEG-400) as a green and recyclable catalyst is described. Our aim is to reduce and control the exothermic nature of this reaction and enhance the yield. This green synthetic approach is highly convenient and safe. The product was isolated with maximum yield (80%). PEG-400, a strongly hydrophilic catalyst can be recyclable for further reactions.

KEYWORDS: Amino acids, PEG 400, substituted benzoyl chloride, N-benzoyl derivatives.

I. INTRODUCTION

The benzoylation of amine and amino acids is well known method to identify, characterize the amines as well as to protect the amino functionality in a multistep synthetic process presented in[1-3]. In addition, the author [4] proposed benzoylation of amino group is used for resolution of amino acids. The N benzoyl derivatives of amino acids can be used as a precursor for various syntheses of potentially active heterocyclic compounds studied in [5-7]. Thus, the development of an efficient and convenient methodology is an important area of research.

There are many methods for preparation of N acyl derivatives of amino acids described in[8-14].The Schotten-Baumann methods [15-20]of benzoylation using benzoyl chloride has wide application and been more preferentially used. During this chemical transformation a smaller addition of sodium hydroxide in benzoyl chloride creates heat and sometimes product is not recovered in [21]. Although a number of reagents, such as benzoyl chloride, benzoic anhydride, benzoyl tetrazole and 2-benzoylthio-1-methylpyridinium chloride were used to carry out this reaction in[22-23].The benzoylation of amino acid by using benzoyl chloride (fischers procedure3 moles benzoyl chlorides per mole of amino acids) in presence of excess sodium bicarbonates was preferably followed[24-25]. Because sodium bicarbonate is a weak alkali facilitate the formation of salts with liberation of carbon dioxide. Further, it was found that the aqueous sodium bicarbonate is non-carcinogenic and more advantageous. It has no hygroscopic characteristic, stability at a wide temperature range, non inflammable, non-volatile, economic, noncorrosive, eco-compatible and devoid of toxic effects. However, the net reaction time and yield of product had been compromised. The benzoyl derivatives so obtained frequently occlude unreacted benzoyl chloride which escapes hydrolysis and poses difficulty in isolating the product. Moreover, to obtain the benzoyl derivative of amino acids, the usual Schotten-Baumann method requires longer reaction time and tedious work-up. The amino acids forms zwitterion ion which make them quite insoluble in organic solvents which make it difficult to synthesis N-acyl derivatives of amino acids rather than the synthesis of simple aliphatic and aromatic amines. Though, there are many methods which are currently used for the preparation of N-acyl derivatives of amino acids and peptides, involve number of steps due to protection and deprotection of carboxylic group of the amino acid.

Considering the importance of benzoylation of amino acids and environmental hazards in the reaction, we have reported the green synthetic approach using PEG400 as a green solvent and catalyst.

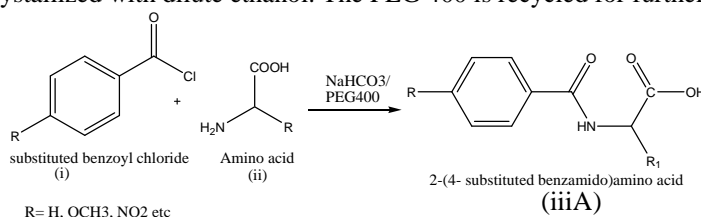
II. EXPERIMENTAL METHODS

All reagents purchased were A.R. grade without further purification. The FTIR spectra were recorded as KBr pellets on Shimadzu Spectrophotometer. Thin layer chromatography (TLC) were performed on 0.2 mm silica gel 60 F254 with plastic support from Aldrich by using various proportion of ethyl acetate and n-hexane as the solvent. ¹HNMR were

recorded on Bruker Avance Neo 500 MHz Spectrometer using TMS as an internal standard and chemical shifts are recorded in δ (parts per million) units with respect to tetra methyl Silane (TMS) as internal standard. Melting points were recorded by open capillaries in liquid bath and uncorrected.

General Procedure for the Preparation of *N*-acyl derivatives of amino Acids

The amino acid (0.01 mol) is dissolved in minimum quantity of saturated sodium bicarbonate (5 ml) solution in a conical flask. Then 50 ml of PEG400 solution was added in conical flask. Slowly substituted Benzoyl chloride added in reaction mixture. The reaction mixture was stirred for fifteen minutes. Then it was kept overnight and poured on crushed ice on next day. Product obtained was (if not formed add very small quantity of acetic acid) filtered and washed with water. It is crystallized with dilute ethanol. The PEG 400 is recycled for further use.



III. RESULTS AND DISCUSSION

In benzoylation of amino acids using strong alkali, the amino acids were dissolved in sodium hydroxide solution and the substituted acyl chloride was added. In reaction mixture, the amino acid is fully transferred to its sodium salt and is soluble in water and there is generation of heat. In the course of the reaction, water-soluble sodium chloride and insoluble *N*-acylamino acid should be formed. The product should be collected by simple filtration. But it was very difficult to obtain the final product as there was formation of substituted benzoic acid, and impurities of amino acids after dilution with acids, ultimately very less amount of product was obtained after filtration. It seems that the presence of amino acid actually catalyzes the hydrolysis of the *N*-acyl derivatives in water media.

With the aim to avoid several steps in the synthesis of *N*-acyl amino acid and formation of benzoic acid, we decided to perform direct *N*-benzoylation of the amino acid with maximum yield. In present method the amino acid is dissolved in minimum quantity of saturated sodium bicarbonate solution. Then 50 ml PEG-400 was added in reaction mixture followed by slow and portion wise addition of substituted benzoyl chloride. In this method, almost 80% yields of the *N*-acyl derivative of amino acids were obtained.

Physical and spectral data

A1:2-(4-nitrobenzamido) acetic acid

Mol. Formula: C₉H₈N₂O₅, Mol. Weight: 224.17, The white crystals product, Yield 85%. The M.P. 192°–193°C; IR 3500, 3150, 2950, 2900, 1750, 1650, and a broad signal 3450–2400 cm⁻¹; ¹H-NMR; (DMSO-d₆), δ 9.20 (1H, t, NH), 8.42 (2H, d, Ar), 8.13 (2H, d, Ar), and 3.95 (2H, d, CH₂); m/z: 224.05 (100.0%), 225.05 (10.0%), 226.04 (1.5%), Elemental Analysis: C, 48.21; H, 3.60; N, 12.50; O, 35.70.

A2:(S)-2-(4-nitrobenzamido)-4-(methylthio) butanoic acid

Mol. Formula: C₁₂H₁₄N₂O₅S, Molecular Weight: 298.31, Yield 86%. M.P. 180°–183°C. IR 3350, 2900, 1750, 1650, 1600, 1550, 1300, and a broad signal at 3300–2400 cm⁻¹; ¹H-NMR (DMSO-d₆), δ 8.50 (1H, d, NH), 8.45 (2H, d, Ar), 8.13 (2H, d, Ar), 4.48 (1H, m, CH), 2.62 (2H, t, CH₂), 2.09 (2H, q, CH₂), and 2.12 (3H, s, CH₃); m/z: 297 (43%), 298 (9%), 299 (100%), 300 (12%), 301 (43%), 302 (30%). Elemental Analysis: C, 48.31; H, 4.73; N, 9.39; O, 26.82; S, 10.75

A3:2-(benzamido)acetic acid

Mol. Formula: C₉H₉NO₃, Molecular Weight: 179.17, Yield 90%. M.P. 189°–191°C. IR 3950, 2850, 3730, 3650, 3600, 3300, 2900, 2850, 1950, 1900, 1850, 1800, 1750, 1600, 1650, and a broad signal at 3900–2700 cm⁻¹; ¹H-NMR (DMSO-d₆), δ 8.85 (1H, t, NH), 7.80 (2H, d, Ar), 7.41 (2H, t, Ar), and 3.96 (1H, d, CH₂); m/z: 179.06 (100.0%), 180.06 (10.3%), 181.06 (1.1%), Elemental Analysis: C, 60.33; H, 5.06; N, 7.82; O, 26.79.

A4:(S)-2-(benzamido)-4-(methylthio) butanoic acid

Mol. Formula: C₁₂H₁₅N₂O₃S, Mol. Weight: 253.32, Yield 85%. The M.P. 177°–178°C. IR 3900, 3750, 3700, 3650, 3630, 3300, 3000, 2950, 1950, 1900, 1850, 1600, and a broad signal at 3900–2600 cm⁻¹; ¹H-NMR (DMSO-d₆) δ 8.47



(1H, d, NH), 7.70 (2H, d, Ar), 7.40 (1H, t, Ar), 7.30 (2H, t, Ar), 4.30 (1H, m, CH), 2.30 (2H, m, CH), 2.06 (2H, t, CH₂), 1.92 (1H, s, CH₃); m/e 61(20%), 105(76%), 206(47%), 236(25%), 253.08 (100.0%), 254.08 (14.1%). Anal. calcd for C₁₂H₁₅NO₃S: C, 56.90; H, 5.97; N, 5.53; S, 12.66, O, 18.95. Found: C, 56.82; H, 6.01; N, 5.49; S, 12.57.

A5:(S)-2-(benzamido)propanoic acid

Mol. Formula: C₁₀H₁₁NO₃, Mol. Weight: 193.20, Yield 90%. IR 3350, 3100, 2950, 1730, 1600 and a broad signal at 3450–2200 cm⁻¹. 1H-NMR (DMSO-d₆), δ 8.48(1H, t, NH), 7.92(2H, d, Ar), 7.50(3H, t, Ar), 3.42(1H, dq, CH), and 2.48(3H, d, CH₃); m/z: 193.05(100.0%), 194.08 (11.1%), 195.07 (1.2%), Elemental Analysis Calcd : C, 62.17; H, 5.74; N, 7.25; O, 24.84, Found: C, 61.75; H, 6.25; N, 7.16, O, 24.84.

A6:(S)-2-(benzamido)-3-phenylpropanoic acid

Mol. Formula: C₁₆H₁₅NO₃, Mol. Weight: 269.30, Yield 88%. The melting point 190°–192°C. IR 3550, 3100, 2900, 2730, 2650, 1650, and a broad signal at 3450–2200 cm⁻¹; 1H-NMR (DMSO-d₆), δ 8.48, 7.92, 7.40, 7.38, 4.40, 1.61, 1.57, and 0.9; m/z: 269.11 (100.0%), 270.11 (17.6%), 271.11 (2.1%), Elemental Analysis Calcd: C, 71.36; H, 5.61; N, 5.21; O, 17.82. Found: C, 71.06; H, 5.71; N, 5.30; O, 17.93.

A7:(2S,3S)-2-(benzamido)-3-methylpentanoic acid

Mol. Formula: C₁₃H₁₇NO₃, Mol. Weight: 235.28, Yield 87%. The M.P. 134°–136°C. IR 3350, 2930, 2900, 2800, 1750, and a broad signal at 3300–2600 cm⁻¹; 1H-NMR (DMSO-d₆), δ 8.39, 7.80, 7.40, 7.33, 4.20, and 0.9; m/z: 235.17(100%), 105(23%), 190(27%), 218(33%), 236(25%). Elemental Analysis: C, 66.36; H, 7.28; N, 5.95, O, 20.41. Found: C, 66.33; H, 7.31; N, 5.90, O, 20.46.

A8:2-(4-methoxybenzamido)-3-phenylpropanoic acid

Mol formula: C₁₇H₁₇NO₄, Mol. Wt :299.32, Yield of pdt 80%. The melting point 180°–185°C. IR 3500, 3200, 2930, 2700, 2620, 1650, and a broad signal at 3450–2200 cm⁻¹; 1H-NMR (DMSO-d₆), δ 8.45, 7.92, 7.27, 7.17, 7.40, 4.72, 3.15, 3.85, 11.00.; m/z: 299.12 (100.0%), 300.12 (18.7%), 301.12 (2.5%), Elemental Analysis: C, 68.21; H, 5.72; N, 4.68; O, 21.38.

A9:2-(4-methoxybenzamido) acetic acid

Chemical Formula: C₁₀H₁₁NO₄, Molecular Weight: 209.20, Yield 85%. M.P. 190°–191°C. IR 3950, 2900, 3600, 3650, 3500, 3300, 2900, 2850, 1850, 1800, 1850, 1830, 1750, 1700, 1600, and a broad signal at 3900–2700 cm⁻¹; 1H-NMR (DMSO-d₆), δ 8.05 (1H, t, NH), 7.94 (2H, d, Ar), 7.20 (2H, t, Ar), and 3.85 (1H, d, CH₂); 3.82(3H, s, CH₃), 11.02(1H, s, OH) m/z: 209.07 (100.0%), 210.07 (11.3%), Elemental Analysis: C, 57.41; H, 5.30; N, 6.70; O, 30.59.

A10:2-(4-methoxybenzamido)propanoic acid

Mol Formula: C₁₁H₁₃NO₄, Molecular Weight: 223.23, Yield of pdt 83%. IR 3350, 3200, 2950, 1750, 1650 and a broad signal at 3450–2250 cm⁻¹. 1H-NMR (DMSO-d₆), δ 8.50(1H, t, NH), 7.92(2H, d, Ar), 7.20(2H, d, Ar), 4.38(1H, dq, CH), 3.84(3H, s, CH₃) 1.45(3H, d, CH₃) and 11.02(H, s, COOH); m/z: 223.08 (100.0%), 224.09 (12.2%), 225.09 (1.5%), Elemental Analysis: C, 59.19; H, 5.87; N, 6.27; O, 28.67.

A11:2-(4-methoxybenzamido)-3-methylpentanoic acid

Mol. Formula: C₁₄H₁₉NO₄, Molecular Weight: 265.30, Yield 90%. The M.P. 130°–135°C. IR 3300, 3100, 2950, 2850, 1700, and a broad signal at 3330–2500 cm⁻¹; 1H-NMR (DMSO-d₆), δ 8.45, 7.94, 7.19, 4.30, 3.85, 2.22, 1.52, 1.12 and 0.90; m/z: 265.13 (100.0%), 266.13 (15.5%), 267.14 (1.9%), Elemental Analysis: C, 63.37; H, 7.22; N, 5.28; O, 24.13.

IV. CONCLUSION

We have concluded that the majority of *N*-benzoyl derivatives of amino acids can be possible to prepare directly from the different amino acid and *p*-methoxy benzoyl chlorides in one-pot syntheses. The procedure is simple addition. There is no need to acidify the reaction mixture in most of cases. This method has many advantages over the traditional methods. There is no need of protection, deprotection, and activation of group. The use of sodium bicarbonate and PEG 400 make it easy, inexpensive and simple. It avoids the formation of side product like substituted benzoic acid and ultimately increase yield.



V. ACKNOWLEDGMENTS

Authors are thankful to UGC WRO, Pune for financial support and the Principal, Shivaji Arts, Commerce and Science College Kannad for availing laboratory facilities.

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