International Journal of Science and Research (IJSR)
ISSN: 2319-7064
ResearchGate Impact Factor (2018): 0.28 | SJIF (2018): 7.426

# Efficient and Green Protocol for the Synthesis of Hippuric Acid

**Sachin S. Fawade[1], Revannath D. Dhokane[2], Dr. Sambhaji Pathare[3], Gitaram Waje[4]**

[1,2,3]Department of Chemistry, LRPD, Arts Science and Commerce College, Rahuri. 413705. (M. S.) India

[4]Professor, Department of Chemistry, LRPD, Arts Science and Commerce College, Rahuri. 413705. (M. S.) India

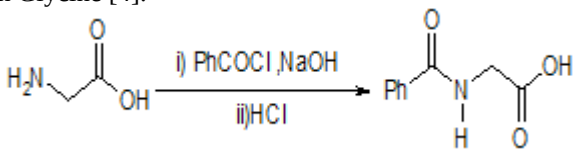
**Abstract:** ***The main aim of the green chemistry to addresses various concerns related to minimization of hazardous chemicals, use of safer green chemicals, catalyst and solvent. A One pot synthesis of Hippuric acid has been achieved starting from Glycine and Benzoyl chloride in the presence of Potassium carbonate as a Green base and Tartaric acid, Citric acid as a Green acid. The recent environmental concerns, we developed the most economical efficient and environmental friendly protocol for the synthesis of Hippuric acid in very good yield (>81%).***

**Keyword:** Hippuric acid, Potassium carbonate, Tartaric acid, Glycine, Citric acid

## 1. Introduction

Amide is an important class in organic compounds. The amide was prepared from organic acid linked to molecule of an amine. In 1824 German chemist Wohler, discovered that the benzoic acid introduced into the stomach which reapers as hippuric acid. Hippuric acid is a α- amino carboxylic acid. Hippuric acid was found in urine [1]. Hippuric acid is a product of reaction of benzoic acid and Glycine. The mechanism involved was the acid –base neutralization process. The amines are acts as a nucleophile instead of base and chlorine anion are becomes a good leaving group. Hippuric acid is an important intermediate and staring materials in many organic synthesis, such as synthesis of 4-arylidene-2-phenyl-5(4h)-oxazolone derivatives (azlactone) [7]-[9].The azlactone scaffolds widely distributed in large number of biologically active compounds. They exhibit different bioactivity such as anticancer [10], antifungal [11], [12], neuroleptic [13], analgesic [11], antibacterial [14], anti-inflammatory [14], antimicrobial [10].

In 1829, Justus von Liebig showed that Hippuric acid was different compound than benzoic acid [1] and its constitution determined [2] in 1834. Later French scientist Victor Dessaignes [3] synthesized Hippuric acid by the action of zinc salt of Glycine and Benzoyl chloride. Modern synthesis of Hippuric acid is done by acylation of benzoyl chloride with Glycine [4].




The recent environmental concerns, we developed the most economical efficient and environmental friendly protocol for the synthesis of Hippuric acid by using different bases like Potassium carbonate, Potassium hydroxide with different acids such as Tartaric acid, Citric acid. In reported work,only used of sodium hydroxide as Base and Hydrochloric acid as an Acid. According to the Hazards Statements [5] Sodium hydroxide and Hydrochloric acid causes severe skin burns and eye damage (H314) and may cause respiratory irritation (H335).For environmental concern we developed green route to synthesized Hippuric acid by using mild organic acid such as Tartaric acid and Citric acid instead of Hydrochloric acid. The $K_2CO_3$ was reported as a green chemical base [6], [7] used instead of sodium hydroxide. This procedure becomes a Green approach for the synthesis of Hippuric acid which is a key important of this work.

## 2. Materials and Methods

All reagents were purchased from commercial sources and used it after purifying. Thin-layer chromatography (TLC) was performed on silica coated glass plate with detection by UV light.$^1$H NMR spectra were recorded with tetramethylsilane as the internal standard. $^1$H NMR spectra were recorded at 400 MHz on bruker. Chemical shift (delta) are reported in ppm downfield from DMSO-$d_6$ (delta = 2.50 ppm) for $^1$H NMR. For $^1$H NMR data are reported as follows: chemical shift, multiplicity (s =singlet, d = doublet, t = triplet, q = quartet, m = multiplet) coupling constant (J) are given in Hz.$^{13}$C NMR spectra were recorded at 100 MHz on bruker. Chemical shift (delta) are reported in ppm downfield from DMSO-$d_6$ (delta = 39.52 ppm) for $^{13}$C NMR. The IR spectra were obtained on lambda scientific FTIR-7600 spectrophotometer using potassium bromide pellets. The ultra violet (UV) spectra were recorded on Systronics AU-2701 UV-Visible Double Beam Spectrophotometer in $CHCl_3$. Melting points were recorded on Digital Melting Point Apparatus (Systronics EQ730).

**Modified Protocol For Synthesis Of Hippuric Acid By Green Route**

Dissolved Glycine (2g, 26.4 mmol) in 1 M aqueous solution of base (10ml Potassium hydroxide base but for Potassium carbonate use of its saturated solution to avoid hydrolysis of benzoyl chloride) in hard glass tube. Add benzoyl chloride (3.10ml, 26.4mmol) in above mixture drop wise simultaneously. After addition, plug the mouth of hard glass test tube with cotton plug, and shake vigorously until the smell of benzoyl chloride does not detected. These mixtures were cooled in ice bath. Acidified the above reaction mixture and stirring the mixtue upto solid crystals were

precipitate, then collected it by filtration and washed with water. Recrystallize by hot water.

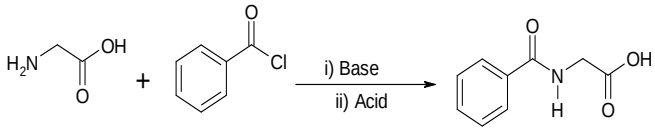



**Table:** Comparative Study of Hippuric acid by Green Route.

| Sr. No. | Compound | Base | Acid | M.P ($^0$C) | Yield% |
|---|---|---|---|---|---|
| 1 | a | $K_2CO_3$ | Tartaric | 188 | 82.00 |
| 2 | | $K_2CO_3$ | Citric | 190 | 83.00 |
| 3 | | $K_2CO_3$ | HCl | 188 | 83.50 |
| 4 | b | KOH | Tartaric | 190 | 81.00 |
| 5 | | KOH | Citric | 186 | 82.50 |
| 6 | | KOH | HCl | 188 | 83.00 |
| 7 | c | NaOH | Tartaric | 188 | 82.50 |
| 8 | | NaOH | Citric | 186 | 82.00 |
| 9* | | NaOH | HCl | 188 | 83.50 |

**9*- Reported Work Used to Comparative Study.**

**Scheme (1a):**
**UV λmax (Chloroform)**: 226 nm, **FTIR (KBr)** υ: 3342.00 (- N-H str.), 3090.00 (-OH stretching.), 2938.00 (-C-H stretching.), 1744.00 (C=O stretching of carboxylic acid), 1603.00, 1556.00 ,1489.00 (C-N str.), 990 (Ar-C-H stretching).**$^1$H NMR (400 MHz, DMSO-$d_6$)** δ (ppm) 12.63 (s, 1H), 8.87 (t, *J* = 5.9 Hz, 1H), 7.98 – 7.85 (m, 2H), 7.64 – 7.33 (m, 3H), 3.96 (d, *J* = 5.9 Hz, 2H).**$^{13}$C NMR (100 MHz, DMSO-$d_6$)** δ (ppm) 171.91, 167.04, 134.34, 131.96, 128.88, 127.77, 41.76

**Scheme (2a):**
**UV λmax (Chloroform)**: 227 nm, **FTIR (KBr)** υ: 3350.00 (- N-H str.), 3080.00 (-OH stretching.), 2920.00 (-C-H stretching.), 1730.00 (C=O stretching of carboxylic acid), 1613.00, 1560.00, 1429.00 (C-N str.), 720 (Ar-C-H stretching).**$^1$H NMR (400 MHz, DMSO-$d_6$)** δ (ppm) 12.60 (s, 1H), 8.87 (t, *J* = 5.9 Hz, 1H), 7.98 – 7.85 (m, 2H), 7.62 – 7.33 (m, 3H), 3.92 (d, *J* = 5.9 Hz, 2H).**$^{13}$C NMR (100 MHz, DMSO-$d_6$)** δ (ppm) 171.91, 167.04, 134.34, 131.96, 128.88, 127.77, 41.76.

**Scheme (3a):**
**UV λmax (Chloroform)**: 226 nm, **FTIR (KBr)** υ: 3340.00 (- N-H str.), 3090.00 (-OH stretching.), 2930.00 (-C-H stretching.), 1735.00 (C=O stretching of carboxylic acid), 1670.00, 1540.00, 1420.00 (C-N str.), 715 (Ar-C-H stretching). **$^1$H NMR (400 MHz, DMSO-$d_6$)** δ (ppm) 12.63 (s, 1H), 8.88 (t, *J* = 5.9 Hz, 1H), 7.98 – 7.86(m, 2H), 7.64 – 7.33 (m, 3H), 3.97 (d, *J* = 5.9 Hz, 2H). **$^{13}$C NMR (100 MHz, DMSO-$d_6$)** δ (ppm) 171.91, 167.04, 134.34, 131.96, 128.88, 127.77, 41.76

**Scheme (4b):**
**UV λmax (Chloroform)**: 226.5 nm, **FTIR (KBr)** υ: 3332.00 (- N-H str.), 3060.00 (-OH stretching.), 2950.00 (-C-H stretching.), 1710.00 (C=O stretching of carboxylic acid), 1608.00, 1516.00, 1419.00 (C-N str.), 790 (Ar-C-H stretching).**$^1$H NMR (400 MHz, DMSO-$d_6$)** δ (ppm) 12.63 (s, 1H), 8.85 (t, *J* = 5.9 Hz, 1H), 7.98 – 7.85 (m, 2H), 7.64 – 7.34 (m, 3H), 3.98 (d, *J* = 5.9 Hz, 2H).**$^{13}$C NMR (100 MHz, DMSO-$d_6$)** δ (ppm) 171.91, 167.04, 134.34, 131.96, 128.88, 127.77, 41.76

**Scheme (5b):**
**UV λmax (Chloroform)**: 226 nm, **FTIR (KBr)** υ: 3360.00 (- N-H str.), 3090.00 (-OH stretching.), 2920.00 (-C-H stretching.), 1720.00 (C=O stretching of carboxylic acid), 1630.00, 1546.00, 1429.00 (C-N str.), 710 (Ar-C-H stretching).**$^1$H NMR (400 MHz, DMSO-$d_6$)** δ (ppm) 12.63 (s, 1H), 8.86 (t, *J* = 5.9 Hz, 1H), 7.98 – 7.85 (m, 2H), 7.64 – 7.33 (m, 3H), 3.94 (d, *J* = 5.9 Hz, 2H).**$^{13}$C NMR (100 MHz, DMSO-$d_6$)** δ (ppm) 171.91, 167.04, 134.34, 131.96, 128.88, 127.77, 41.76

**Scheme (6b):**
**UV λmax (Chloroform)**: 227 nm, **FTIR (KBr)** υ: 3345.00 (- N-H str.), 3070.00 (-OH stretching.), 2910.00 (-C-H stretching.), 1710.00 (C=O stretching of carboxylic acid), 1660.00, 1560.00, 1420.00 (C-N str.), 710 (Ar-C-H stretching).**$^1$H NMR (400 MHz, DMSO-$d_6$)** δ (ppm) 12.63 (s, 1H), 8.85 (t, *J* = 5.9 Hz, 1H), 7.98 – 7.85 (m, 2H), 7.64 – 7.33 (m, 3H), 3.93 (d, *J* = 5.9 Hz, 2H).**$^{13}$C NMR (100 MHz, DMSO-$d_6$)** δ (ppm) 171.91, 167.04, 134.34, 131.96, 128.88, 127.77, 41.7

**Scheme (7c):**
**UV λmax (Chloroform)**: 226 nm, **FTIR (KBr)** υ: 3330.00 (- N-H str.), 3090.00 (-OH stretching.), 2990.00 (-C-H stretching.), 1700.00 (C=O stretching of carboxylic acid), 1620.00, 1546.00, 1420.00 (C-N str.), 710 (Ar-C-H stretching). **$^1$H NMR (400 MHz, DMSO-$d_6$)** δ (ppm) 12.63 (s, 1H), 8.87 (t, *J* = 5.9 Hz, 1H), 7.98 – 7.85 (m, 2H), 7.64 – 7.33 (m, 3H), 3.96 (d, *J* = 5.9 Hz, 2H).**$^{13}$C NMR (100 MHz, DMSO-$d_6$)** δ (ppm) 171.91, 167.04, 134.34, 131.96, 128.88, 127.77, 41.76

**Scheme (8c):**
**UV λmax (Chloroform):** 226 nm, **FTIR (KBr)** υ: 3360.00 (- N-H str.), 3070.00 (-OH stretching.), 2930.00 (-C-H stretching.), 1740.00 (C=O stretching of carboxylic acid), 1620.00, 1560.00, 1420.00 (C-N str.), 720 (Ar-C-H stretching).**$^1$H NMR (400 MHz, DMSO-$d_6$)** δ (ppm) 12.63 (s, 1H), 8.87 (t, *J* = 5.9 Hz, 1H), 7.96 – 7.85 (m, 2H), 7.64 – 7.33 (m, 3H), 3.95 (d, *J* = 5.9 Hz, 2H).**$^{13}$C NMR (100 MHz, DMSO-$d_6$)** δ (ppm) 171.91, 167.04, 134.34, 131.96, 128.88, 127.77, 41.76

## 3. Result and Discussion

This is a modified protocol for synthesis of Hippuric acid. The key feature of this protocol is the use of green base and acids. In this modified protocol, we used green base Potassium carbonate and unreported base potassium hydroxide instead of reported work on Sodium hydroxide (H314) [5].Hydrochloric acid (H314 & H335) [5] used for acidification in reported synthesis of Hippuric acid. For minimisation of these hazards, we used green acids such as, Tartaric acid [15] and Citric acid [16].

In reported work, Hippuric acid was synthesized by using Hydrochloric acid and Sodium hydroxide. The yield of Hippuric acid is very good but this was not a green route. We developed the green protocol and observed that all the reactions underwent very smoothly to furnish the Hippuric acid with very good yield.

This is the most efficient and environmental friendly procedure. The ***Scheme- 9*c*** is the reported work having 83.50% yield. This reported scheme is used for comparison with remaining present work, ***a-(1, 2, 3), b - (4,5,6), c - (7,8)***. The ***Scheme - a1*** and ***a2*** is novel work i.e. green protocol, for synthesis of Hippuric acid. ***Scheme- a3*** proved that, $K_2CO_3$ is suitable Green Base instead of reported NaOH base; Similarly, ***Scheme- b6*** proved that, KOH is suitable base instead of reported NaOH base. Tartaric acid and Citric acid are naturally occurring Green acids, which are used in green protocol to synthesized Hippuric acid. This is proved that in ***Scheme - c7*** and ***c8.*** In present work all Scheme gives satisfactory yield (> 81%).The structures of Scheme- ***a-(1, 2, 3), b - (4,5,6), c- (7,8)*** were confirmed by spectroscopic technique ($^{13}$C NMR & $_1$H-NMR).

## 4. Conclusion

In conclusion, we have developed highly efficient, eco-friendly and Green protocol for the synthesis of Hippuric acid. The protocol gives access to the synthesis of Hippuric acid by using Green acids and Green base in very good yield in short reaction time.

## 5. Acknowledgement

Authors thanks to, Loknete Ramdas Patil Dhumal,Arts, Science and Commerce College, Rahuri, Ahmednagar (M.S.) for the financial assistance. Author thank to S. A. Pathare and G. V. Waje for useful discussion during the preparation of manuscript. Author also thank to P.K. Warghude for providing spectroscopic data.

## References

[1] Liebig, Justus (1829) “Ueber die saurewelche in demHarn der grans fressen denvierfussigen thiereen thaltenist” (On the acid which is contained in the urine of grass-eating, four- footed animals), Annalen der Physik und Chemie, 17:389-399.
[2] Liebig, Justus (1834) “Ueber die Zusammensetzung der Hippurasaure” (On the composition of Hippueic acid),Annalen der Physik und Chemie,32:573-574.
[3] Dessaignes V.(1853). “Ueber die Regeneration der Hippursaure” (On the regeneration of hippuric acid). AnnalenderChemieundPharmacie.87(3):352-327. doi:10.1002/jlac.18530870311.
[4] Ingersoll, A.W.;Babcock S.H.(1932).“Hippuric acid” Organic synthesis.12:40. Doi.10.15227/ orgsyn. 012.0040. Collective Volume,2, p. 328.
[5] AdamMickiewicz,University,*http://www.staff.amu.edu.pl/~psorg/serp.pdf* (accessed April 2013).
[6] Mazaahir Kidwai, Manohar Lal, Neeraj Kumar Mishra and Anwar Jahan. Green Chemistry Letters and Reviews, 2013, Vol. 6, No. 1, 63-68.
[7] Sachin S. Fawade, Dr. Sambhaji Pathare, Revannath D. Dhokane, Prof. Gitaram Waje,“Efficient And Green Route To Access 4- Arylidene-2-Phenyl-5(4h)-Oxazolone Derivatives (Azlactone)” 2019 IJRAR June 2019, Volume 6, Issue 2, IJRAR19K7568, p. 167-171.
[8] Plochl, *Ber, 16, 2815, (1883)*
[9] Erlenmeyer Ann 275.1, (1892)
[10] Philip S, et al, New colorimetric cytotoxic assay for anti-cancer drug screening. J National Cancer Inst 1990; Vol. 82, 1107-1112.
[11] Jakeman D.L, Farrell S, Young N, Doucet RJ, Timmons SC, Novel jadomycins incorporation of non-natural and natural amino acids. Bioorg Med Chem.Lett 2005; Vol. 15, No. 5, pp. 1447-1449.
[12] Sah P, Nair S, Garg SP, Synthesis and antimicrobial activity of some new oxazolone derivatives of 4,5-disubstituted -2-aminothiazole. J Indian ChemSoc 2006; Vol. 83, No. 2, 205-207.
[13] Cascio G, Manghisi E., Fregnan G, 5-Piperazinylalkyl-2(*3H*)-oxazolones with neuroleptic activity. J. Med. Chem. 1989, Vol. 32, No. 10, 2241-2247.
[14] Crespo MI, et al, Synthesis and biological evaluation of 3, 4-diaryloxazolonnes: A new class of orally active cyclooxygenase-2 inhibitors. J Med Chem 2000; Vol. 43, No. 2, 214-223.
[15] Farzaneh Mohamadpour, Malek Taher Maghsoodlou, Majtaba Lashkari, Reza Heydari, Nourallah Hazeri , “Green synthesis of Poysubstituted Quinolines and Xanthene derivatives Promoted by Tartaric acid as a naturally green catalyst under solvent free condition” Chemistry Journal of Moldova . Issue: 2018 Vol. 13, No.1, p. 74-86.
[16] Monika Patil,Shrikrishna Karhale, Ananada Kundale, Arjun Kumbhar, Sagar More and Vasant Helavi, “Green protocol for the synthesis of 1,8-dioxo-decahydroacridines by Hantzsch condensation using citric acid as organo-catalyst” CURRENT SCIENCE, Vol.116, No.6,25 March 2019.