Synthesis of hippuric acid – Protocol D

$$NH_2CH_2COOH + C_6H_5COCl + 2NaOH + HCl \rightarrow C_6H_5CONHCH_2COOH + 2NaCl + 2H_2O$$

Reaction. Dissolve 3 g (40 mmol) of glycine in its equivalent of 1M sodium hydroxide solution in a 200 or 300 mL flask. Place a piece of litmus paper in the flask and add in small portions a quantity of benzoyl chloride about 15% in excess of that required by theory to react with the glycine. After adding each portion, shake well until all of the chloride has reacted. The mixture must be kept slightly alkaline, with the aid of additional sodium hydroxide if necessary. Cool the reaction mixture under the tap if it gets warm. Finally eliminate paper or other solid material by filtration, and then place in the solution a piece of Congo red indicator paper. Using an eyedropper, and stirring the reaction mixture effectively, add just enough dilute (6M) hydrochloric acid to turn the Congo red paper from deep red to purple. Cool the flask and allow the mixture to stand for 10 minutes or more.

Isolation. Collect the resulting crystalline precipitate of hippuric acid upon the Büchner funnel and dry in a vacuum desiccator.

Purification. When the crystals are thoroughly dry, place in about 25 mL of carbon tetrachloride and boil very gently in a beaker under a watch glass for about 5 minutes. Filter the mixture while hot, and repeat the treatment. Finally wash the crystals with ethyl ether and dry again in the desiccator.

Safety. Synthesis should be performed in a fume hood. See hazards associated with the reagents in Table 1.

Greenness Assessment. The evaluation was performed using the Green Star (GS) and the results are shown in Figure 1.

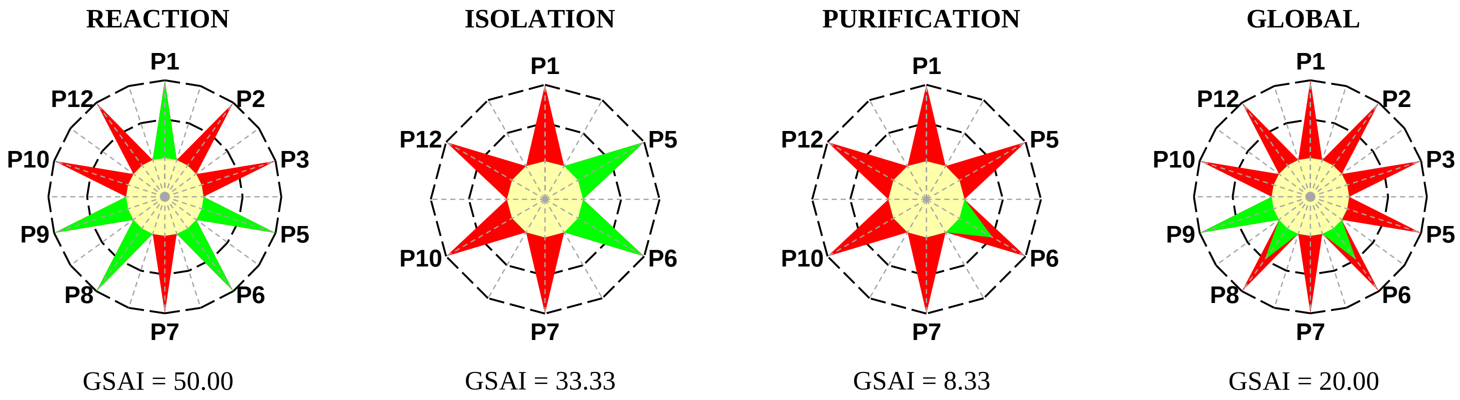

Figure 1. Greenness assessment (GS) for the synthesis of hippuric acid

Construction of the GS

$$NH_2CH_2COOH + C_6H_5COCl + 2NaOH + HCl \rightarrow C_6H_5CONHCH_2COOH + 2NaCl + 2H_2O$$

Table 1 presents the hazards and scores associated with the substances involved and Table 2 presents the scores used to construct the green stars.

Table 1. Hazards for the synthesis of hippuric acid, protocol D$^{\alpha}$

Substances involved	Step			Hazard code	Score: hazards to...		
	R	I	Pu		HH	E	P
Stoichiometric reagents							
Benzoyl chloride (CAS 98-88-4)	✓			H302, H312, H314, H317, H332	3	1	1
Glycine (CAS 56-40-6)	✓			-	1	1	1
Hydrochloric acid (6M solution)	✓			H315, H319, H335	2	1	1
Sodium hydroxide (1M solution)	✓			H314	3	1	1
Auxiliary substances							
Solvents							
Carbon tetrachloride (CAS 56-23-5)			✓	H301, H311, H331, H351, H372, H412	3	2	1
Ethyl ether (CAS 60-29-7)			✓	H224, H302, H336, EUH019, EUH066	2	1	3
Product							
Hippuric acid (495-69-2)	✓	✓	✓	H302, H315, H318, H335	3	1	1
Waste							
Benzoic acid			✓	H318, H335	3	1	1
Benzoyl chloride (excess)		✓		H302, H312, H314, H317, H332	3	1	1
Carbon tetrachloride			✓	H301, H311, H331, H351, H372, H412	3	2	1
Ethyl ether			✓	H224, H302, H336, EUH019, EUH066	2	1	3
Hydrochloric acid (dilute solution)		✓		-	1	1	1
Sodium chloride (aqueous solution)		✓		-	1	1	1
Water[a,b]		✓		-	1	1	1

$^{\alpha}$ R – Reaction; I – Isolation; Pu – Purification; HH – Human Health; E – Environment; P – Physical

[a] Renewable; [b] Degradable to innocuous products

Table 2. Scores used to construct the green star for the synthesis of hippuric acid, protocol D[α]

Green Chemistry Principle	Reaction		Isolation		Purification		Global	
	s	Explanation	s	Explanation	s	Explanation	s	Explanation
P1 Prevention	3	Without waste	1	Excess of benzoyl chloride, H314	1	Benzoic acid, H318, and carbon tetrachloride, H301, H311, H331, H351, H372	1	Excess of benzoyl chloride, H314, benzoic acid, H318, and carbon tetrachloride, H301, H311, H331, H351, H372
P2 Atom Economy	1	Excess of stoichiometric reagents > 10%, formation of by-products		NA		NA	1	Excess of stoichiometric reagents > 10%, formation of by-products
P3 Less hazardous chemical synthesis	1	Benzoyl chloride, sodium hydroxide, H314, hippuric acid, H318		NA		NA	1	Benzoyl chloride, sodium hydroxide, H314, hippuric acid and benzoic acid, H318, carbon tetrachloride, H301, H311, H331, H351, H372
P5 Safer solvents and auxiliary substances	3	Solvents and auxiliary substances are not used	3	Solvents and auxiliary substances are not used	1	Carbon tetrachloride, H301, H311, H331, H351, H372	1	Carbon tetrachloride, H301, H311, H331, H351, H372
P6 Increase energy efficiency	3	Room temperature	3	Room temperature	2	0 ºC ≤ T ≤ 100 ºC	2	0 ºC ≤ T ≤ 100 ºC
P7 Use renewable feedstocks	1	Substances not renewable	1	Substances not renewable	1	Substances not renewable	1	Substances not renewable
P8 Reduce derivatives	3	One stage		NA		NA	2	Two stages
P9 Catalysts	3	Without catalysts		NA		NA	3	Without catalysts
P10 Design for degradation	1	Substances not degradable	1	Substances not degradable	1	Substances not degradable	1	Substances not degradable
P12 Safer chemistry for accident prevention	1	Benzoyl chloride, sodium hydroxide, H314, hippuric acid, H318	1	Hippuric acid, H318, and excess of benzoyl chloride, H314	1	Carbon tetrachloride, H301, H311, H331, H351, H372, hippuric acid and benzoic acid, H318, and ethyl ether, H224, EUH019	1	Benzoyl chloride, sodium hydroxide, H314, hippuric acid and benzoic acid, H318, carbon tetrachloride, H301, H311, H331, H351, H372, and ethyl ether, H224, EUH019

[α]s – Score; NA – Not applicable

References

Robertson, G.R. *Laboratory Practice of Organic Chemistry – 3rd edition*. The Macmillan Company: New York, 1954, pp. 328-329.