Synthesis of hippuric acid – Protocol C

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

Reaction. Dissolve 2.5 g (33 mmol) of glycine in 25 mL (83 mmol) of 10% sodium hydroxide solution (about 26% excess) contained in a conical flask. Add 5.4 g (38 mmol) of benzoyl chloride (about 15% excess) in two portions to the solution. Shake vigorously after each addition until all the chloride has reacted. Transfer the solution to a 100 mL beaker and rinse the conical flask with a little water. Place a few grams of crushed ice in the solution and add concentrated hydrochloric acid, slowly and with stirring until the mixture is acid to Congo red paper.

Isolation. Collect the resulting crystalline precipitate of hippuric acid, upon a Büchner funnel, wash with cold water and drain well.

Purification. Place the solid in a 100 mL beaker with 10 mL of carbon tetrachloride, cover the beaker with a watch glass and boil the mixture gently for 5 minutes. Allow the mixture to cool slightly, filter by gentle suction, and wash the hippuric acid on the filter with 3-4 mL of carbon tetrachloride. Recrystallize from boiling water (about 75 mL) with the addition of a little decolorizing carbon if necessary, filter through a hot water funnel, and allow to crystallize. Collect the pure hippuric acid in a Büchner funnel and dry it in the steam oven.

Safety. 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.

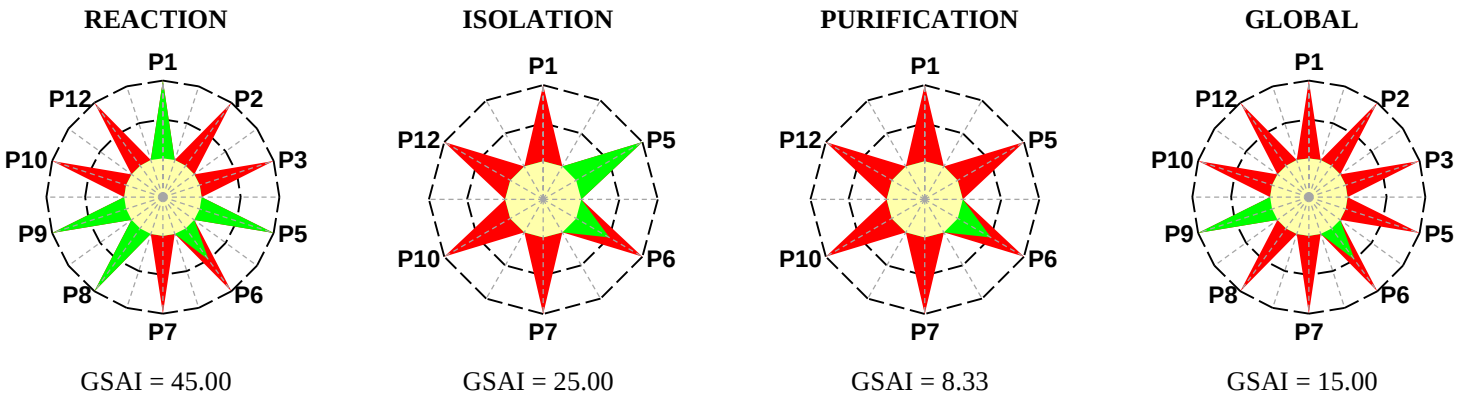

Figure 1. Greenness assessment (GS) for the synthesis of hippuric acid

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 C[α]

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 (CAS 7647-01-0)	✓			H314, H335	3	1	1
Sodium hydroxide (10% solution)	✓			H314	3	1	1
Auxiliary substances							
Solvents							
Carbon tetrachloride (CAS 56-23-5)			✓	H301, H311, H331, H351, H372, H412	3	2	1
Water[a,b]	✓	✓	✓	-	1	1	1
Other auxiliary substances							
Decolorizing carbon (CAS 7440-44-0)			✓	-	1	1	1
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
Decolorizing carbon			✓	-	1	1	1
Hydrochloric acid (dilute solution)		✓		-	1	1	1
Sodium chloride (aqueous solution)		✓		-	1	1	1
Water[a,b]		✓	✓	-	1	1	1

[α] 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 C[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 and hydrochloric acid, H314, hippuric acid, H318		NA		NA	1	Benzoyl chloride, sodium hydroxide and hydrochloric acid, H314, hippuric acid and benzoic acid, H318, carbon tetrachloride, H301, H311, H331, H351, H372
P5 Safer solvents and auxiliary substances	3	Water	3	Water	1	Carbon tetrachloride, H301, H311, H331, H351, H372	1	Carbon tetrachloride, H301, H311, H331, H351, H372
P6 Increase energy efficiency	2	0 ºC ≤ T ≤ 100 ºC	2	0 ºC ≤ T ≤ 100 ºC	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	1	Three 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 and hydrochloric acid, H314, hippuric acid, H318	1	Hippuric acid, H318, and excess of benzoyl chloride, H314	1	Carbon tetrachloride, H301, H311, H331, H351, H372, and hippuric acid and benzoic acid, H318	1	Benzoyl chloride, sodium hydroxide and hydrochloric acid, H314, hippuric acid and benzoic acid, H318, and carbon tetrachloride, H301, H311, H331, H351, H372

[α]s – Score; NA – Not applicable

References

Vogel, A.I. *Elementary Practical Organic Chemistry*. Longmans, Green and Co: London, 1958, pp. 244.