Synthesis of hippuric acid

Evaluation of protocols including a preliminary step of preparation of reagents

Protocol E[1]

The greenness assessment made for protocol E did not include the preparation of reagents. If this step is considered to the greenness, the final evaluation corresponds to Figure 1. Table 1 presents the hazards and scores associated with the substances involved and Table 2 presents the scores used to construct the green stars.

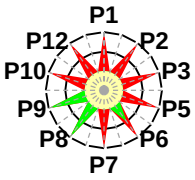
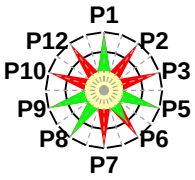
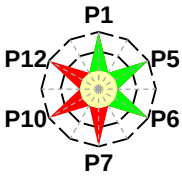
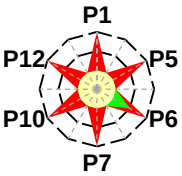
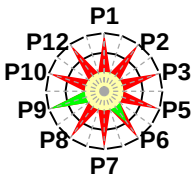
PREPARATION OF REAGENTS	REACTION	ISOLATION	PURIFICATION	GLOBAL
				
GSAI = 25.00	GSAI = 45.00	GSAI = 50.00	GSAI = 8.33	GSAI = 15.00

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

Table 1. Hazards for the synthesis of hippuric acid, protocol E[α]

Substances involved	Step				Hazard code	Score: hazards to...		
	Prep	R	I	Pu		HH	E	P
Stoichiometric reagents								
Ammonium hydroxide (concentrated solution)	✓				H290, H314, H335, H400	3	3	2
Benzoyl chloride (CAS 98-88-4)		✓			H302, H312, H314, H317, H332	3	1	1
Chloroacetic acid (CAS 79-11-8)	✓				H301, H311, H314, H331, H400	3	3	1
Glycine (CAS 56-40-6)		✓			-	1	1	1
Hydrochloric acid (CAS 7647-01-0)		✓			H314, H335	3	1	1
Sodium hydroxide (CAS 1310-73-2)		✓			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
Sodium hydroxide (CAS 1310-73-2)	✓				H314	3	1	1
Product								
Hippuric acid (495-69-2)		✓	✓	✓	H302, H315, H318, H335	3	1	1
Waste								
Ammonia	✓				H221, H280, H314, H331, H400	3	3	2
Ammonium chloride (aqueous solution)	✓				-	1	1	1
Ammonium hydroxide (aqueous solution)	✓				-	1	1	1
Benzoic acid				✓	H318, H335	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] Prep – Preparation of reagents; 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 E[α]

Green Chemistry Principle	Preparation of reagents		Reaction		Isolation		Purification		Global	
	s	Explanation	s	Explanation	s	Explanation	s	Explanation	s	Explanation
P1 Prevention	1	Ammonia gas, H314, H331, H400	3	Without waste	3	Waste is innocuous	1	Benzoic acid, H318, and carbon tetrachloride, H301, H311, H331, H351, H372	1	Ammonia gas, H314, H331, H400, benzoic acid, H318, and carbon tetrachloride, H301, H311, H331, H351, H372
P2 Atom Economy	1	Excess of ammonia > 10%, formation of by-products	1	Excess of hydrochloric acid > 10%, formation of by-products		NA		NA	1	Excess of ammonia and of hydrochloric acid > 10%, formation of by-products
P3 Less hazardous chemical synthesis	1	Chloroacetic acid, H301, H311, H314, H331, H400, ammonia, H314, H331, H400, and sodium hydroxide, H314	1	Benzoyl chloride, sodium hydroxide and hydrochloric acid, H314, hippuric acid, H318		NA		NA	1	Chloroacetic acid, H301, H311, H314, H331, H400, ammonia, H314, H400, 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	1	Sodium hydroxide, H314	3	Water	3	Solvents and auxiliary substances are not used	1	Carbon tetrachloride, H301, H311, H331, H351, H372	1	Sodium hydroxide, H314, and carbon tetrachloride, H301, H311, H331, H351, H372
P6 Increase energy efficiency	2	0 ºC ≤ T ≤ 100 ºC	2	0 ºC ≤ T ≤ 100 ºC	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	1	Substances not renewable
P8 Reduce derivatives	3	One stage	3	One stage		NA		NA	1	Four stages
P9 Catalysts	3	Without 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	1	Substances not degradable
P12 Safer chemistry for accident prevention	1	Chloroacetic acid, H301, H311, H314, H331, H400, ammonia, H314, H400, and sodium hydroxide, H314	1	Benzoyl chloride, sodium hydroxide and hydrochloric acid, H314, hippuric acid, H318	1	Hippuric acid, H318	1	Carbon tetrachloride, H301, H311, H331, H351, H372, hippuric acid and benzoic acid, H318	1	Chloroacetic acid, H301, H311, H314, H331, H400, ammonia, H314, H400, Benzoyl chloride, sodium hydroxide and hydrochloric acid, H314, hippuric acid and benzoic acid, H318, carbon tetrachloride, H301, H311, H331, H351, H372

[α]s – Score; NA – Not applicable

References

(1) Blatt, A.H. et al. *Organic Syntheses, collective volume II*. John Wiley & Sons, Inc.: New York, 1959, pp. 328-330.