Synthesis of hippuric acid

Greenness optimization

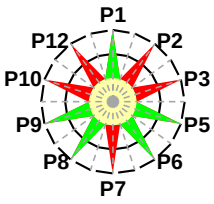
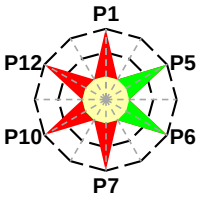
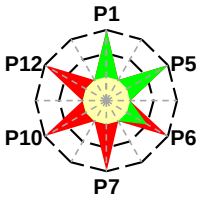
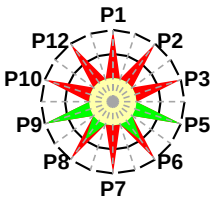
The greenest procedures for each step are R_4^1 for the reaction, I_4^2 for the isolation, and Pu_1^3 for the purification. Combining these procedures it is possible to obtain greener procedures than those of the original protocols.

In Table 1 is presented the combination of the greener procedures. This combination corresponds to a protocol greener than any one of the analysed (GSAI = 30.00).

It is worth to note that the GS for the isolation of the product is not equal to the GS of the greener procedure (I_4), because excess of stoichiometric reagents higher than 10% is used in the reaction R_4, which will be separated from the product during the isolation. Since one of the reagents in excess is the benzoyl chloride which presents high hazard to human health, the score of P1 in the GS of the isolation is minimal.

The optimized protocol is described below.

Table 1. Green star obtained by combining the greenest procedures of each step

Combination	Reaction	Isolation	Purification	Global process
	R_4	I_4	Pu_1	
1				
	GSAI = 50.00	**GSAI = 33.33**	**GSAI = 41.67**	**GSAI = 30.00**

Optimized protocol

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. Filter the precipitate and dry.

Purification. Transfer the solid to a beaker, add 25 mL of ethanol, and heat on a boiling water bath until complete dissolution. Leave the solution to crystallize and then cool in an ice bath for a few minutes. Filter the crystals by suction and wash with 10 mL of cold ethanol. Dry the product in an oven at a temperature below 100 ºC for 15 minutes.

References

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

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

(3) Universidade de Aveiro, *http://www.ua.pt/ensino/PageDisc.aspx?id=2528* (accessed April 2011).