Synthesis of acetanilide

Greenness optimization

The greenest procedures for each step are: R_8[1] and R_9[1] for the reaction, I_6[1,2] for the isolation, and Pu_1,[3] Pu_2,[2] Pu_4,[4,5] Pu_7[6] and Pu_9[1] for the purification. Combining these procedures it is possible to obtain greener procedures than those of the original protocols.

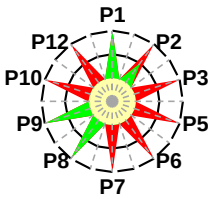
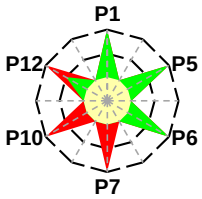
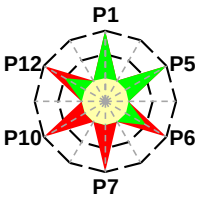
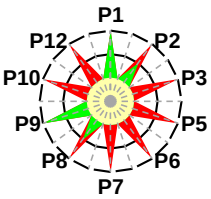
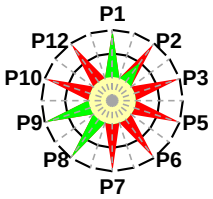
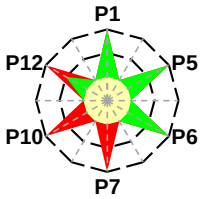
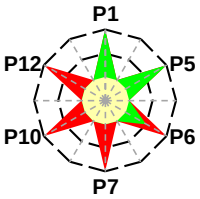
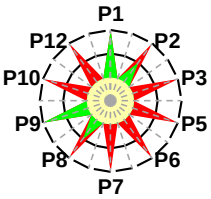
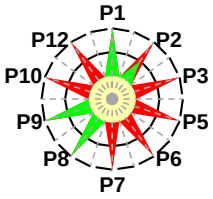
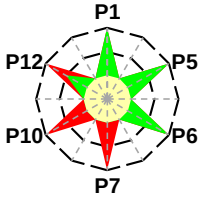
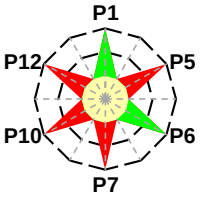
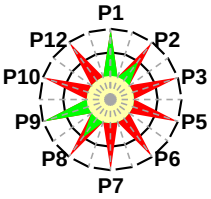
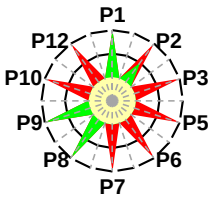
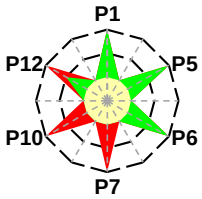
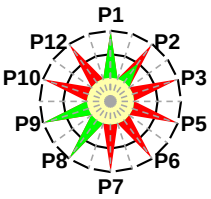
In Table 1 are presented four combinations (1-4), considering the greener procedures for the reaction and isolation and different procedures for the purification, with GSAI values between 33.33 and 50.00. Combination 3 coincides with protocol L,[1] the greenest of the evaluated (GSAI = 30.00).

The combinations 1, 2 and 3 present all the same greenness (GSAI = 30.00). However, despite the global greenness being the same in all combinations, it should not be indifferent the choice of the procedures for the several steps, because the greenness in each step is itself relevant. In this case, one should choose the purification procedures Pu_1, Pu_2, Pu_4, Pu_7 or Pu_9.

Combination 4 is the greenest (GSAI = 35.00), because purification is not prescribed. This combination is greener than any of the analysed protocols.

Optimized protocols are described below.

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

Combination	Reaction	Isolation	Purification	Global process
1	R_8, R_9  GSAI = 35.00	I_6  GSAI = 58.33	Pu_1, Pu_2, Pu_4, Pu_7, Pu_9  GSAI = 50.00	 GSAI = 30.00
2	R_8, R_9  GSAI = 35.00	I_6  GSAI = 58.33	Pu_3, Pu_5, Pu_{11}  GSAI = 41.67	 GSAI = 30.00
3 = Pr L	R_8, R_9  GSAI = 35.00	I_6  GSAI = 58.33	Pu_8  GSAI = 33.33	 GSAI = 30.00
4	R_8, R_9  GSAI = 35.00	I_6  GSAI = 58.33	Without purification	 GSAI = 35.00

Optimized protocol 1

Reaction. Add 20 mL of a mixture of equal volumes of acetic anhydride (106 mmol) and glacial acetic acid to 10 mL (110 mmol) of aniline (stoichiometric proportions) contained in a 150 mL conical flask. Fit a reflux water-condenser to the flask, and boil the mixture gently for 10 minutes. Then pour the hot liquid into 200 mL of cold water, stirring the latter well during the addition.

Isolation. Filter the acetanilide at the pump, and wash well with water.

Purification. Transfer the filtrated crystals into a 250 mL beaker, and add 100 mL of hot water. Heat this solution until complete dissolution. If coloured and/or insoluble impurities are observed,

add about 0.5 g of activated charcoal. Boil for 5 to 10 minutes. Filter the solution on a Büchner funnel previously heated in an oven. Allow to cool. Filter the crystals on a Büchner funnel and wash with two portions of 5 mL of cold water. Dry the crystals in an oven at 80 ºC.

Optimized protocol 2

Reaction. Add 20 mL of a mixture of equal volumes of acetic anhydride (106 mmol) and glacial acetic acid to 10 mL (110 mmol) of aniline (stoichiometric proportions) contained in a 150 mL conical flask. Fit a reflux water-condenser to the flask, and boil the mixture gently for 10 minutes. Then pour the hot liquid into 200 mL of cold water, stirring the latter well during the addition.
Isolation. Filter the acetanilide at the pump, and wash well with water.
Purification. Recrystallize the acetanilide from a large volume of water containing a little ethanol.

Optimized protocol 3

Reaction. Add 20 mL of a mixture of equal volumes of acetic anhydride (106 mmol) and glacial acetic acid to 10 mL (110 mmol) of aniline (stoichiometric proportions) contained in a 150 mL conical flask. Fit a reflux water-condenser to the flask, and boil the mixture gently for 10 minutes. Then pour the hot liquid into 200 mL of cold water, stirring the latter well during the addition.
Isolation. Filter the acetanilide at the pump, and wash well with water.
Purification. Recrystallize the product from about 60 mL of a mixture of one volume of acetic acid and two volumes of water. Filter off the colourless crystals at the pump, again wash thoroughly with water, drain, and dry.

Optimized protocol 4

Reaction. Add 20 mL of a mixture of equal volumes of acetic anhydride (106 mmol) and glacial acetic acid to 10 mL (110 mmol) of aniline (stoichiometric proportions) contained in a 150 mL conical flask. Fit a reflux water-condenser to the flask, and boil the mixture gently for 10 minutes. Then pour the hot liquid into 200 mL of cold water, stirring the latter well during the addition.
Isolation. Filter the acetanilide at the pump, and wash well with water.
Purification. Not prescribed.

References

(1) Mann, F.G.; Saunders, B.C. *Practical Organic Chemistry - 4th edition*. Longmans, Green and Co: London, 1960, pp. 107.
(2) Fieser, L.F. *Experiments in Organic Chemistry - 3rd edition*, D.C. Heath and Company: Boston, 1955, pp. 151-152.
(3) Universidade de Aveiro, *http://www.ua.pt/ensino/PageDisc.aspx?id=2524* (accessed April 2011).
(4) Mayo, D.W.; Pike, R.M.; Butcher, S.S. *Microscale Organic Laboratory*. John Wiley & Sons, Inc.: New York, 1986, pp. 192-195.
(5) Durst, H.D.; Gokel, G.W. *Experimental Organic Chemistry - 2nd edition*. McGraw-Hill Book Company: New York, 1987, pp. 367-369.
(6) Universidade Federal de Santa Catarina, *http://www.qmc.ufsc.br/organica/docs/QMC5230_apostila_12_Exp.pdf* (accessed April 2013).