Extraction of Hydrazine by Selective Precipitation: Process Flow-Sheet

Ahmad El hajj*, Anne-Julie Bougrine and Henri Delalu
Université de Lyon – Université Claude Bernard Lyon 1
Laboratoire Hydrazines et Composés Energétiques Polyazotés – UMR 5278 ;
"UCBL/CNRS/CNES/SNPE"
43, bd du 11 novembre 1918 – 69622 Villeurbanne Cedex
ahmad.el-hajj@adm.univ-lyon1.fr

This study relates to an improved process devoted to the preparation of an endocyclic hydrazine, the pyrazolidine (PYRZ, $C_3H_8N_2$), in order to develop a versatile and flexible method, more suitable for an industrial scale and which can be implemented in batch or continuously process, according to the desired tonnage. This synthesis way is based on a transposition of the Raschig process, by the action of sodium hypochloride on 1,3-diaminopropane at room temperature, then recovering of the hydrazine formed. The overall process of synthesis, extraction and purification of pyrazolidine was established and optimized and a process flow-sheet was proposed.

1. Introduction

The endocyclic hydrazines are used in several fields, mainly in the pharmaceutical and cosmetic industries. In particular, pyrazolidine (**1**, **PYRZ**, $C_3H_8N_2$) is a precursor of 2-(2-(S)-Amino-3-methylpentanoyl)pyrazolidine-1-carboxylic acid (3-nitrophenyl) amide, used in the treatment of type 2 diabetes, by inhibition of the dipeptidyl peptidase IV (DPP-IV) (Hyae Gyeong Cheon et al. (2005)). In cosmetics, it is involved in the synthesis of derivatives of 1-alkyl-4,5-diamino-pyrazole, developed by the Wella Society (1992), which can be used as hair dyes.

Two methods of pyrazolidine synthesis were described in the literature:

1. Synthesis by the Raschig process, method developed by Luttringhaus et al. (1959) involving the reaction between diaminopropane and sodium hypochloride: the pyrazolidine was not isolated but was mixed to benzensulfonyl to give a derivative with a yield of 33%.

2. Synthesis from 1,3-dibromopropane and hydrazine: this process is unsuitable for industrial purposes (Crawford (1966) and Hasegawa et al. (1998)).

2. Synthesis of the pyrazolidine by modified Raschig process

Currently, the most satisfactory way for the environment for the synthesis of hydrazine is the Raschig process (Raschig (1907a and 1907b), Omietanski et al. (1956) and Jain et al. (1985)), which presents many advantages: minimal pollution (chemicals in water without organic solvent, whether for the synthesis or for the extraction), economic gain (inexpensive reagents: sodium hypochloride, diaminopropane), fast reaction rates, selectivity and feasibility of a continuous transposition.

In the case of pyrazolidine, the Raschig synthesis can be schematized by the two successive reactions detailed in figure 1.
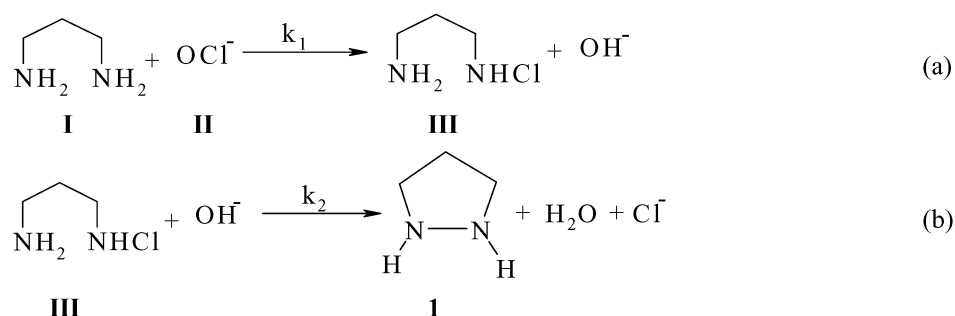
$$\underset{\textbf{I}}{\text{NH}_2\text{—NH}_2} + \underset{\textbf{II}}{\text{OCl}^-} \xrightarrow{k_1} \underset{\textbf{III}}{\text{NH}_2\text{—NHCl}} + \text{OH}^- \qquad \text{(a)}$$

$$\underset{\textbf{III}}{\text{NH}_2\text{—NHCl}} + \text{OH}^- \xrightarrow{k_2} \underset{\textbf{1}}{\overset{}{\text{N}\text{—}\text{N}}} + \text{H}_2\text{O} + \text{Cl}^- \qquad \text{(b)}$$

Figure 1: Reaction mechanism of the formation of pyrazolidine

This synthesis is then carried out in two steps:
Step 1: oxidation of 1,3-diaminopropane (**I**, DAP, $C_3H_{10}N_2$) by sodium hypochloride (**II**) and formation of the N,chloro-1,3-diaminopropane (**III**).
Step 2: cyclization of N,chloro-1,3-diaminopropane (**III**) in order to obtain pyrazolidine (**1**). This synthesis requires an excess of the diaminopropane (DAP) reagent ($[DAP]_0/[OCl^-]_0 = 8$), in comparison with the sodium hypochloride, in order to increase the yield in pyrazolidine to 80%.

2.1 Experimental sections
Reagents:
1,3-diaminopropane: supplied by Acros® ; Sodium hypochloride: provided by Arkema® ; Water was purified by circulation on an ion-exchange resin.

The synthesis of pyrazolidine in stoichiometric conditions ($[DAP]_0/[OCl^-]_0 = 1$) was performed according to the following procedure:
17.6 g of 1,3-diaminopropane (0.237 mol) were introduced in a thermostated reactor at 298K. 100 ml of an aqueous NaOCl solution (0.214 mol), contained in a bulb, were added dropwise during 20 minutes. The reactor temperature during the addition of bleach evolves between 298 and 303K. The reaction was complete when all the diaminopropane reagent disappeared, which was detected by gas chromatography. Analysis of the reaction mixture gave a yield of 34% (quantitative GC/MS).

The formation reaction of pyrazolidine is competed with parallel reactions, which limits the yield to 34%. In order to increase the yield of pyrazolidine, an excess of the DAP aminating reagent must be used, as underlined in the following table.

Table 1: Experimental results = evolution of the yield of pyrazolidine according to the initial molar ratio of reagents p = [DAP]$_0$/[OCl$^-$]$_0$

$p = (\dfrac{[DAP]_0}{[OCl^-]_0})$	[DAP]$_M$ in the reaction mixture mol.l^{-1}	[OCl$^-$]$_M$ in the reaction mixture mol.l^{-1}	Yield of pyrazolidine %
1.11	1.96	1.76	34,4
2.04	3.20	1.57	50,1
4.16	5	1.2	66,6
8.27	6.95	0.84	80
11.75	5.87	0.5	85
20	8	0.4	86

3. Extraction

For the extraction process, these non-stoichiometric synthesis conditions imply then the (pyrazolidine / diaminopropane) separation and the recycling of the excess amine upstream of the synthesis. However, this is particularly difficult because of the very close physicochemical properties of these two compounds. In particular, the boiling temperatures of pyrazolidine (411 K, 1 bar) and 1,3-diaminopropane (409-410 K, 1 bar) differ by only 1 to 2 K, which leads to avoid implementing distillation operations.

Several solutions are thus possible: a precipitation of one of the two compounds as a hydrochloride salt by addition of hydrochloric acid, a selective phase transfer in a suitable solvent or a selective crystallization of the pyrazolidine. We chose the first option. In order to show the feasibility of this step, we determine and set three isothermal sections (283 K, 298 K and 333 K) of the isobaric solid-liquid ternary system DAP.2HCl /Water/PYRZ.2HCl by ITA (Isoplethic Thermal Analysis).

3.1. Isoplethic Thermal Analysis

This original method was developed in our laboratory (Tenu and Counioux (1983), Berthet and Counioux (1993)). It consists to follow the evolution of one or more physical properties of the system when its composition is modifying. For this study, liquid-solid equilibria were obtained by ITA, a device which permits to underline the transformations (crystallization, solubilization of a solid phase) of the system, in the course of addition of pure water for a constant reference temperature T_R. Thus, the molar and mass compositions of the mixture evolve in a linear way during the analysis and determine so an isoplethic section in the ternary system.

The fluctuation of the temperature is obtained using the following equation:

$$\Delta T = (S. \Delta H_D - \Delta H_d).V/K$$

Where:
S: solubility (g of substance/liter of solvent)

ΔH_D: weight enthalpy of dissolution (J.g^{-1} of substance)

ΔH_d: partial volumic enthalpy of dissolution (J.l^{-1} of substance)

V: rate of injection (ml.h^{-1})

K: cell constant (W.K^{-1})

3.2. Experimental

Figure 2 represents a thermogram obtained by ITA for a mixture whose composition M is located in the invariant ternary triangle (Figure 3). It shows the evolution of the temperature during the addition of pure water to the mixture M.
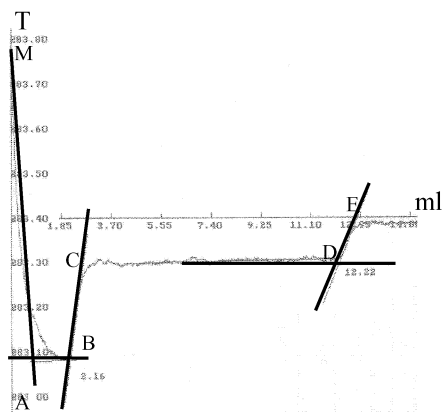

Figure 2: Thermogram obtained by ITA,
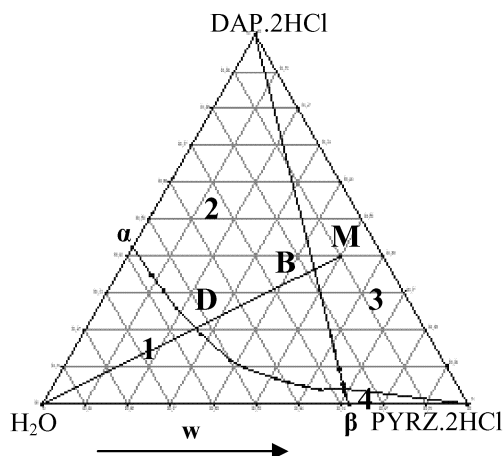$T = f (v_{H2O})$
(P = 1 atm, T= 283K)

Figure 3: DAP.2HCl /H₂O/PYRZ.2HCl solid-liquid ternary system determinated by Isoplethic Thermal Analysis at P= 1 atm and T = 283 K.

Segment MA corresponds to the equilibrium of the triphasic system M. From A to B, the addition of pure water implies the dissolution of the PYRZ.2HCl salt. At point B, the last crystals of dihydrochloride pyrazolidine disappear. Segment CD corresponds to the solid-liquid equilibrium between the saturated liquid and the DAP.2HCl salt. At point D, the last crystals of dihydrochloride diaminopropane dissolve. Segment DE corresponds to the dilution of the system and the return to the equilibrium temperature. The B and D points correspond then to the end of dissolution of each salt.

We denoted α, the solubility of the DAP.2HCl in pure water and β, the solubility of PYRZ.2HCl in pure water at 283K. All the isotherms studied (283, 298 and 333 K) are characterized by 4 equilibria:

- a liquid phase in the water rich part (1: L).
- a biphasic domain of crystallization of DAP.2HCl (2: L + DAP.2HCl$_{(s)}$)
- an invariant triphasic triangle (3: L$_i$ + DAP.2HCl$_{(s)}$ + PYRZ.2HCl$_{(s)}$).
- a biphasic domain of crystallization of PYRZ.2HCl (4: L + PYRZ.2HCl$_{(s)}$)

Table 2: Massic compositions of the invariant liquid L_i, as function of the temperature

T/K	%w PYRZ.2HCl	%w DAP.2HCl	%w H$_2$O
283	68.2	2.9	28.9
298	68.8	4.1	27.1
333	71	7.5	21.5

By this method, we can thus recycle a majority of the DAP reagent used in the synthesis. In particular, at 283 K, it is possible to precipitate and recycle 98% of the diaminopropane involved in the synthesis. We obtain then an aqueous solution of pyrazolidine dihydrochloride titrating 68 %w PYRZ.2HCl. A final purification by selective crystallization is implemented in order to obtain high purity PYRZ.

4. Conclusions and process flow-sheet

The synthesis process of pyrazolidine by reaction of 1,3-diaminopropane with sodium hypochloride, involves the following steps, shown in figure 4.

a) Reaction of diaminopropane with sodium hypochloride in aqueous medium in order to form pyrazolidine (p= [DAP]$_0$/[OCl$^-$]$_0$ = 8).

b) Demixing of the reaction mixture obtained in step (a) by addition of anhydrous NaOH and recovering of the organic phase.

c) Precipitation of the diaminopropane dihydrochloride (DAP.2HCl) salt by addition of hydrochloric acid.

d) Evaporation of excess water and filtration of the DAP.2HCl salt.

e) Neutralization of the DAP.2HCl by addition of two equivalents of sodium hydroxide in order to obtain molecular diaminopropane which is then recycled after distillation.

e) Evaporation and filtration of the aqueous solution of pyrazolidine dihydrochloride.

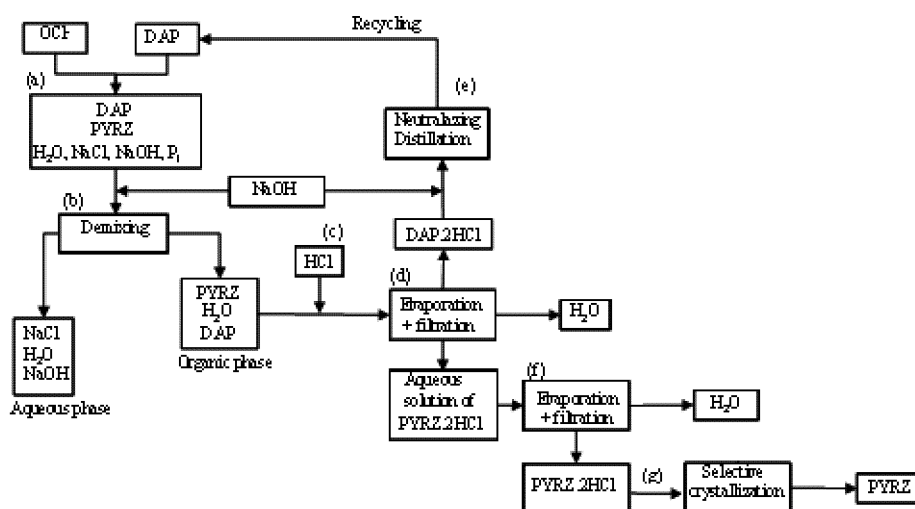g) Final purification by selective crystallization in order to obtain high purity PYRZ.

Figure 4: Process flow-sheet

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