An Investigation on the Synthesis of 2,4,6-trichloropyrimidine-5-carbaldehyde

ADRIAN BARBATU[1], CRISTINA POP[1], STEFAN TOMAS[1]*

[1] University Politehnica of Bucharest, Faculty of Applied Chemistry and Materials Science, Department of Bioresources and Polymer Science, 149 Calea Victoriei 149, 010072, Bucharest, Romania

2,4,6-trichloropyrimidine-5-carbaldehyde is a versatile intermediate in the synthesis of reactive dyes. Starting from a previously described obtaining method of this compound, we have investigated the influence of reaction conditions on the final yield.

Keywords: 2,4,6-trichloropyrimidine-5-carbaldehyde, Vilsmeier synthesis, azomethinic dyes

The chemistry of synthetic dyes diversified in the middle of the '50 of the XX century with the discovery and manufacture of a new class of dyes – the reactive dyes – compounds in which the cromophore group is directly linked, by a covalent bond, to the substrate which is to be dyed.

The general structure of a reactive dye according to H. Zollinger [1] is as follows:

W-D-Q-RG-X, where:

D represents the chromogen;

RG is a reactive group;

Q is a linking group;

X is a leaving group;

W is a hydrophilic group.

The role of the reactive group (RG) is to permit the formation of the covalent bond between the dye and the substrate and in the same time to act as a "separator component" between the chromogen and the leaving group. The separator component is a group that does not allow a modification of the conjugation in the region of the chromogen, thus maintaining its absorbtion maximum in its initial position. It must also permit the bonding of the nucleophilic groups in the natural substrates (wool, silk, cotton, linen etc) –OH, -NH_2 or –SH groups in the protein fibers and –OH groups in the polysaccharose fibers [2].

Taking into account the reaction mechanisms that involve nucleophilic reagents, only two of them qualify: the aromatic nucleophilic substitutions and the nucleophilic additions to double carbon-carbon bonds of the general structure –Y-CH=CH_2, where Y is a strong electron attracting group, the main representative being the vinyl-sulphonic dyes, a class largely marketed (-SO_2-CH=CH_2).

Other existing examples, for instance those which react by several addition and elimination reactions, for instance the α-bromo-acrylamide group, rely on the same mechanisms.

The over 50 years experience in research and marketing reactive dyes in which the aromatic nucleophilic substitution is used, showed that there are several linking groups of great interest:

-2,4,6-trichloro-1,3,5-triazine (cyanuric chloride) derivatives;

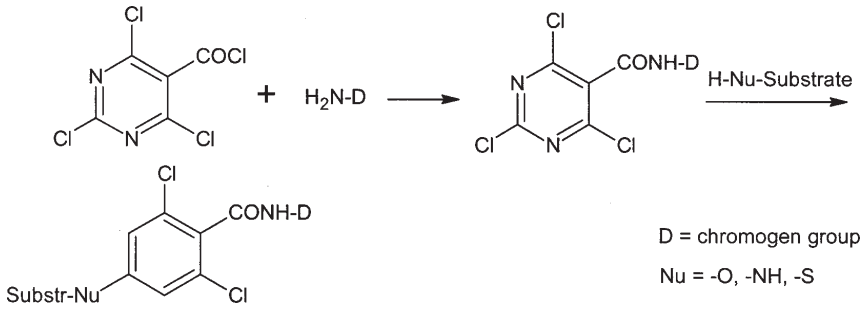
-2,4,6-trihalogeno-pyrimidine derivatives;

-2,3-dichloro-quinoxaline derivatives.

Each one of these linking groups has their advantages and disadvantages regarding to reactivity, stability towards hydrolysis of the formed covalent bonds etc.

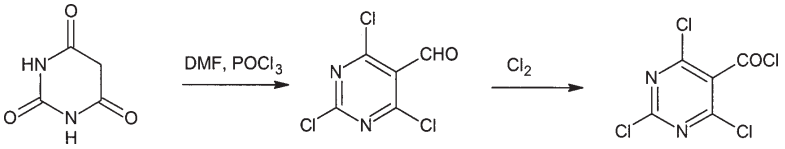
One of the problems which appear in the case of 2,4,6-trihalogenopyrimidine derivatives are related to the reactivity of the three halogen atoms: the formation of the bond between the chromogen group and the link group may involve practically any of the three atoms, which is a handicap to obtain different dyes.

In order to avoid this behaviour, it was proposed the synthesis of a new link group, the acid chloride of the 5-carboxilic-2,4,6-trichloro-pyrimidinic acid [3]. The reactivity of the acid chloride group is different from the reactivity of halogen atoms. The chromogen, containing a free amino group, reacts with the acid chloride in the link group to form a 5-(chromogen-amide) derivative which will be subsequently linked to the substrate by the substitution of one of the chlorine atoms.



Scheme 1. Fixation to substrate

* *email: aastomas@hotmail.com; Tel.: +40214022705*



Scheme 2. Dehnert synthesis

Dehnert proposed a synthesis of the link group starting from barbituric acid. By means of a Vilsmeier reaction, a formyl group is inserted in the position 5 of the barbituric acid, then the –OH groups in the barbituric acid are replaced by halogen atoms in the presence of phosphorous oxychloride. The formyl group is later oxidized to carboxylic group in the presence of chlorine and the acid chloride is formed. The reaction is presented in the scheme 2.

Remarkably, the formation of 2,4,6-trichloro-pyrimidine-5-carbaldehyde is made in a one-pot reaction, in a time-temperature controlled reaction, using an excess of $POCl_3$. After the 5-formyl derivative is formed, the temperature is increased to 85^{0}C and the reaction mixture is maintained at this temperature for 20h.

We were interested to study this reaction in order to find out if the reaction yield varies according to the reaction conditions and to optimize each step.

Experimental part

Materials and methods

The general synthesis of 2,4,6-trichloropyrimidine-5-carbaldehyde was performed according to the synthesis proposed in [3] using reagent degree pure chemicals acquired from Merck and Sigma-Aldrich. The reagent degree dimethylformamide was purified to eliminate traces of ammonia by fraction distillation with benzene and water.

We characterized the compounds by means of FT-IR spectra. The FT-IR spectra were recorded on a Jasco 6200 spectrometer equipped with a Specac Golden Gate attenuated total reflectance (ATR) accessory, using a resolution of 4 cm^{-1} and an accumulation of 60 spectra, in the 4000-400 cm^{-1} wave number region [5].

We have conducted a number of four experiments, with the intent to study the dependence of yield upon temperature and duration of each reaction step.

In the first experiment we mixed phosphorous oxychloride and dimethylformamide (7:1 mol) at room temperature, then added barbituric acid under vigorous stirring and increased the temperature to 50^{0}C where it was kept for 6 h. Finally, we increased the temperature to 85^{0}C for 15 h.

In the second experiment we added phosphorous oxychloride to dimethylformamide (8:1 mol) and cooled the mixture on an ice bath. Subsequently, we added barbituric acid under vigorous stirring and slowly increased the temperature to 50^{0}C where it was carefully maintained for 6 h. In the final step, we increased the temperature again slowly to 85^{0}C and kept it constant for 20 h.

In the third experiment we added phosphorous oxychloride to dimethylformamide (7:1 mol) cooled on an ice bath. We added barbituric acid under vigorous stirring and heated the mixture at 50^{0}C for 4 hours. Finally, we increased the temperature to 85^{0}C for 15 h.

The fourth experiment was carried out in the same conditions as the second experiment, but this time phosphorous oxychloride was removed by distillation at the end of the reaction.

The laboratory equipment consisted of a three neck round bottom flask equipped with a mixing mechanism, reflux condenser, gas burner and ice/water bath.

In each experiment the precipitate was collected by filtration on a Büchner funnel.

After each step at 50^{0}C we have collected a sample from the reaction mass, processed in order to isolate the

Table 1
YIELD vs TEMPERATURE AND TIME

Experiment No.	(Het)*:$POCl_3$:DMF molar ratios	Temperature (^{0}C)	Time (hrs)	$POCl_3$ Distilled (Y/N)	Yield (%)	Notes
1.	1:7:1	20	–	No	30	The $POCl_3$-DMF mixture was not sufficiently cooled.
		50	6			
		85	15			
2.	1:8:1	<10	–	No	46	–
		50	6			
		85	20			
3.	1:7:1	<10	–	No	10	The time intervals for the 50 ^{0}C and 85 ^{0}C were changed.
		50	4			
		85	15			
4.	1:7:1	<10	–	Yes	0	The distillation time was probably too long, leading to destruction of useful compound
		50	6			
		85	20			

* Het= barbituric acid

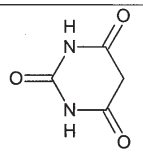
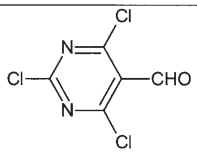
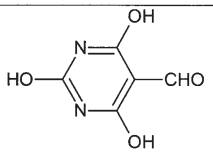
No.	Compound	Structure
a)	barbituric acid	
b)	2,4,6-trichloropyrimidine-5-carbaldehyde	
c)	2,4,6-trihydroxypyrimidine-5-carbaldehyde	

Table 2
LIST OF COMPOUNDS INVOLVED IN THE SYNTHESIS

Compound	Wave number (cm^{-1})	Attribution
a)	3183	-N-H
	2872	-C-H
	1679	-C=O
	3079	-C-H
b)	2703	-C-H in formyl
	1716	-C=O in formyl
	1575	-C=N in pyrimidine
	673	-C-Cl
c)	2991	-C-H aromatic
	2822	-C-H in formyl
	1720	-C=O in formyl
	1601	-C=N

Table 3
FT-IR SPECTRA

formed 5-formyl-derivative of the barbituric acid and analyzed it by IR spectrophotometry in order to check if the synthesis of formyl group was successful.

The melting point of the obtained 2,4,6-trichloro-pyrimidine-5-carbaldehyde was determined to be ~130-131 ^{0}C [4], using a Boetius apparatus.

Results and discussions

The variation of yield on reaction times and temperatures is presented in the table 1.

One may notice that the best yield is obtained in Experiment no. 2 (46%), with a short step below 10^{0}C, a 6-hour step at 50^{0}C and a 20-hour step at 85^{0}C.

a) The relevant peaks are at 3183 cm^{-1} which corresponds to -N-H bond, 3079 cm^{-1} which may be attributed to aromatic -C-H, 1679 cm^{-1} indicates -C=O bond.

b) The relevant peaks are at 2703 cm^{-1} which may be attributed to –C-H bond in formyl group. 1716 cm^{-1} peak corresponds to -C=O in formyl group, while 1575 cm^{-1} may be attributed to -C=N and -C=C in pyrimidine ring. The peak at 673 cm^{-1} may indicate -C-Cl bond. The IR spectrum confirms that the synthesis of 2,4,6-trichloro-pyrimidine-5-carbaldehyde was successful.

c) The peak at 2822 cm^{-1} corresponds to -C-H in formyl group, while the peak at 1720 cm^{-1} may be attributed to -C=O in formyl group. The peak at 1601 cm^{-1} indicates -C=N and -C=C bonds in pyrimidine ring. There is no peak in the lower region of the spectrum which could be attributed to -C-Cl, so we can conclude that in the 50^{0}C step only the formyl group is formed and the chlorine atoms are not attached in this step (table 3).

Conclusions

Starting from a previously described synthesis we wished to check the influence of reaction conditions such as temperature and duration of each step on the yield of the final product. We have determined that cooling the reagents mixture below 10^{0}C in the first step is of utmost importance, leading to a significant yield increase (46% vs 30%). The formation of the Vilsmeier reagent requires low temperatures. Also, shortening the duration of the subsequent steps causes an even sharper decrease of the yield (46% vs 10%).

Based on our observations, we can conclude that any modification in either temperature or duration of each step leads to obtaining a lower yield for the final product.

Acknowledgements: The work has been funded by the Sectorial Operational Programme Human Resources Development 2007-2013 of the Romanian Ministry of Labour, Family and Social Protection through the Financial Agreement POSDRU/88/1.5/S/61178.

References

1.ZOLLINGER, H., Color Chemistry, VCH, Weinheim, New York, Basel, Cambridge, 1991, p. 168
2.HUNGER, K., Industrial Dyes: Chemistry, Properties, Applications, Wiley-VCH, Weinheim, 2003, p 113
3.DEHNERT, J. Ger. Offen. DE 3603797, 1987 (Chem. Abstr. 1988, 108, 7511z)
4.BĂRBATU A., STANCU I.C., MITRAN R.A., TOMAS St., "Reactive dyes derived from 2,4,6-trichloro-5-formyl pyrimidine", UPB Sci.Bull, Series B, **73**, Iss. 4, 2011
5.MITRAN, R.A, BOSCORNEA, A.C., STANCU I.C., TOMAS, St., "Some unusual spectral properties of 6-azauracil derivatives", in UPB Sci. Bull., Series B, **73**, Iss. 1, 2011

Manuscript received; 7.11.2012

review

ALKALOIDS. REPRESENTANTIVES. BIOACTIVITY

by

Camelia Şoldea, Anca Mihaela Mocanu

Publishing House: Matrix Rom, Bucharest, 2013

The authors of the book "ALKALOIDS. REPRESENTATIVES. BIOACTIVITY", Assoc. Prof. dr. eng. Camelia Şoldea and Lecturer dr. eng. Anca Mihaela Mocanu belong to the teaching staff of the Faculty of Chemical Engineering and Environmental Protection, Technical University "Gheorghe Asachi" of Iasi, Department of Organic, Biochemical and Food Engineering. The book is focused on a subject of a high interest for the scientific research and university education, that of natural bioactive products, the alkaloids among them.

As natural compounds of vegetable or animal origin the alkaloids are biosynthesized by a quite impressive number of species all over the world being constantly studied for elucidating their features crucial for the characterization of biologically active products.

The eight chapters of the present book covering 325 pages are devoted to the most significant groups of alkaloids encountered in different geographic areas all over the world. The first chapter presents the general aspects quite necessary for an extensive approach of the alkaloids: classification, occurrence in nature, chemical structures and bioactivity, structure-activity correlations, uses in traditional and modern medical applications, metabolic conversions and biogenesis.

In the following chapters, 11 groups of the most significant heterocyclic alkaloids are discussed as derivatives of: pyrrolizidine, indolizidine, quinolizidine, indole, quinoline, isoquinoline, tropane, piperidine, pyridine, pyrrolidine and purine.

Every group of alkaloids is clearly described as regards the classification and main representatives, occurrence in various vegetable and animal species and also in marine organisms specified for various families, genera and species, the characteristic properties and bioactivities correlated with the particularly complex and various structures as well as the biosynthetic ways as revealed by the scientific papers reported in recent years. Attention is also paid to the action mechanisms and to the conversion schemes advanced by different authors for metabolic pathways and biogenesis. According to literature cited, some new alkaloid groups and individual compounds and their significance are presented, such as the Calistegines (Cap. V).

Many pharmacological properties are displayed by the numerous vegetable families mentioned in the present book: Apocynaceae, Amaryllidaceae, Loganiaceae, Rubiaceae, Puniaceae, Pandanaceae, Clavicipitaceae and many others discussed with every alkaloid group. The Penicillium, Aspergillus and other fungi species as well as the marine organisms are also paid attention to. Many effective pharmacological activities shown by the botanical species as well as by their extracts and other preparations are cited by the authors. Thus, anti-inflammatory, antimicrobial, antiviral, anti-parasitic, anti-oxidative, analgesic properties, activities against tumor cell lines as well as the benefic actions in case of cardio-vascular, digestive and skin diseases deserve mention. The anti-AIDS properties are also frequently noticed, even in cases where other medical treatments fail. The positive effects on the central nervous system (CNS), mental diseases, the Alzheimer's disease among them, are also important for various therapies making use of the alkaloids and the vegetables they are contained in.

The toxic effects of many alkaloid groups with the main representatives responsible for that are described in every chapter where the danger to the human health and the environment are pointed out.

The vast and up-to-date literature cited with every chapter is well connected to the book sections providing high-level and useful information to the readers allowing them to go deeply into the various domains of interest in their educational and research activities.

The book content and the approaching manner are illustrative for a monographic work of an uniqueness character in our country and of a high scientific level among other works in the world. The professors and the students, including the master and Ph.D. ones, the researchers and other people of university education as chemists and biochemists, chemical engineers, biologists, medical specialists as those involved in food industry, environmental protection and agriculture sciences could take advantage of the book "ALKALOIDS. REPRESENTANTIVES. BIOACTIVITY" by Camelia Şoldea and Anca Mihaela Mocanu in their activities.

Prof. em. chem. Constantin Luca , Ph.D.

Technical University "Gheorghe Asachi"of Iasi
Faculty of Chemical Engineering and Environmental Protection