8-7-2003

Preparation of Pyridinium and Diaminocarbonium Barbituric Acid Ylides

Frederic Douelle
University of New Orleans

PREPARATION OF PYRIDINIUM AND DIAMINOCARBONIUM BARBITURIC ACID YLIDES

A Thesis

Submitted to the Graduate Faculty of the
University of New Orleans
in partial fulfillment of the
requirements for the degree of

Master of Science
in
The Department of Chemistry

by

Frederic Douelle

D.U.T, University of Poitiers (France), 2000
Bsc (Hons), Manchester Metropolitan University (U.K), 2001

August 2003

ACKNOWLEDGEMENTS

First I would like to thank to my research advisor, Branko Jursic, for his help and advice. When I came to University of New Orleans, I did not know anything about organic chemistry. I still do not know much but Branko showed me the beauty of this field of chemistry and for this I will always be grateful.

I would also like to thank Bruce Gibb, Guijun Wang, Mark Trudell, and John Wiley to be part of my committee.

I am indebted to the group members, Paresh Patel, Donna Newman, and Kate Bowdy, for their scientific support and friendship. It has been a real pleasure to work in this lab.

Finally, a special thanks for Dr Stevens who carried out the X-ray structure analysis.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

ABSTRACT

Through NMR experiments of the reaction of barbituric acid with carbodiimide, a general synthetic procedure for the preparation of 5-diaminomethylenebarbiturates (**DABA**) was developed. This procedure is very simple and applicable to the preparation of large quantities of **DABA** derivatives. Through the X-ray structural study of one of the **DABA** derivatives it was established that these compounds have a ylide-type structure with strong charge separation inside the molecule. 5-Ylide-pyridinium-methyl barbituric acid derivatives were investigated with the isolation of 4-dimethylamino-1-(2,4,6-trioxo-hexahydro-pyrimidin-5-ylide-methyl)-pyridinium as well as its corresponding 1,3-dimethylbarbituric acid derivative with quantitative yields. An alternative approach was attempted in order to prepare chiral 5-ylide-pyridinium-methyl-barbituric acid derivatives thus containing a chiral center between the charge separation. The extreme instability of the derivatives under investigation afforded the unique isolation of 4-dimethylamino-1-[(1,3-dimethyl-2,4,6-trioxo-hexahydro-pyrimidin-5-yl)-phenyl-methyl]-pyridinium in quantitative yield.

1. YLIDES

1.1 General Remarks

Although the first preparation and isolation of an ylide compound was done by Michael and Gimborn in 1884, the term "ylid" was first coined in the German language by Georges Wittig in 1944[1]. It was derived by use of the ending *–yl* to imply an open valence (i.e., meth*yl*) and the ending *–id* to imply anionicity (i.e., acetyl*id*) both on a carbon atom. Subsequently the term "ylid" most often has been translated into the English form "ylide", which will be used throughout. An ylide[2] can be defined as a substance in which a carbanion is attached directly to a heteroatom carrying a high degree of positive charge, represented by the general formula **I**. (**Figure 1**). This definition also takes into account those resonance hybrid molecules in which there is an important contributing structure. Therefore, ylides may have an enolate structure **II** (**Figure 1**). Although, the molecular system **III** (**Figure 1**) carries less than a formal full positively charged structure, the latter structure can be included into the definition of ylides too.

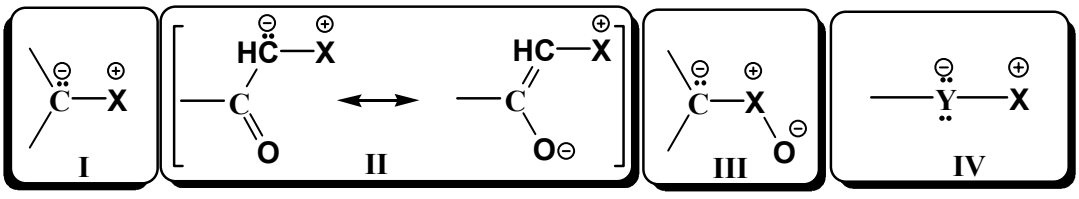


Figure 1. Four groups of organics ylides.

From chemical and physical properties, as well as by virtue of molecular structure point of view, the onium heteroatom general structure **IV** (**Figure 1**) is similar to the ylide structure. These substances are isoelectronic with ylides, and the two classes of compounds exhibit a remarkable similarity in properties.

Special characteristics of ylides making them worthy of study includes their unique stabilization afforded by the carbanions and the presence of the adjacent onium atom group. Thus, many ylides have been isolated as crystalline, stable substances whereas normal carbanions are seldom isolatable and are very reactive toward atmospheric conditions.

Ylides undergo two basic types of reactions; those in which only the carbanion is involved mechanistically and those in which both the carbanion and the heteroatom are involved. The first group consists of those reactions where any carbanion, regardless of structure, would react in conditions such as alkylation, acylation, direct attack toward electrophiles, or even nucleophilic attack toward unsaturated groups. The presence of the heteroatom portion of the ylide is usually reflected only in its effect on the nucleophilicity undertaken by the carbanion. The usefulness of ylides in this type of reaction is based mainly on their availability in a wide variety of structural environments. Since carbanion reactions inevitably are those which allow the formation of new carbon-carbon bonds, the availability of almost any carbanion without worry of isomeric possibilities has been applied to synthetic organic chemistry. However, perhaps the most interesting reactions of ylides belong to the second group, which involves both the carbanion and the heteroatom portion.

1.2 Phosphonium and Sulfonium Ylides

1.2.1 Stability

Phosphonium ylides have a general structure often written as a resonance hybrid (**Figure 2**). The minimum structural requirement for a phosphonium ylide is that it contains an anionic carbon attached to a phosphorus atom which carries a high degree of positive charge.

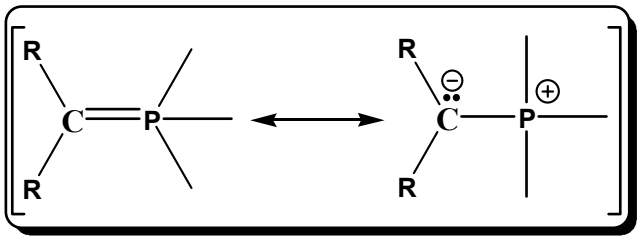


Figure 2. Phosphonium ylides molecular structure.

As would be expected on the basis of the above general formula, these substances are reactive and therefore are challenging to isolate. However, the fact that some phosphonium ylides have sufficient stability to be capable of isolation has been attributed to the structural and electronic factors which contribute to stabilization of the ylidic carbanion. This stabilization has been thought to result from delocalization of the non-bonded electrons of the carbanion. By examining the phosphonium ylide structure again (**Figure 2**), stabilization of the carbanion could be afforded by both the phosphonium heteroatom (P) and the two carbanion substituents (R). Thus, it is apparent that the ability of the group R to delocalize the carbanionic electrons does affect the stability of the ylides. Nevertheless, it is clear that this stabilization is not sufficient in itself to account for the unique stability of phosphonium ylides. It was shown that the use of the vacant

3d-orbital of the phosphorus atom provides a stabilization effect due to the phosphorus atom expansion of its outer shell to accommodate more than eight electrons. Experimental evidence indicates that phosphorus can use its 3d-orbitals in σ bonding making the the phosphorus atom pentavalent[3].

Noting the discussion about the existence and stabilization of phosphorus ylides, it would be expected that any other molecular system containing the same general structural features and a heteroatom group which is capable of providing adequate stabilization for a carbanion should form a yilde of some finite existence.

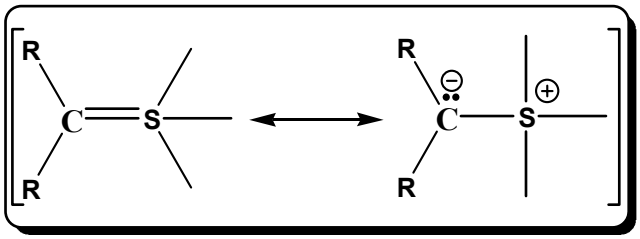


Figure 3. Sulfonium ylides molecular structure.

Considerable experimental evidence has accumulated the fact that the sulfonium salt is extremely effective in stabilizing an adjacent carbanion, as shown on the molecular system **Figure 3**. Some estimate that stabilization is based on conjugative electron-accepting ability of the sulfur atom[4] from its vacant 3d-orbital overlap.

Therefore, in terms of stability and structure, phosphonium and sulfonium ylides are essentially equal.

1.2.2 Reactivity toward carbonyl group

One of the widest applications of phosphorus ylides is the condensation-elimination reaction with an aldehyde or ketone to form an olefin and a phosphine oxide (**Figure 4**). The unique and well-known reaction is named Wittig reaction. The mecha-

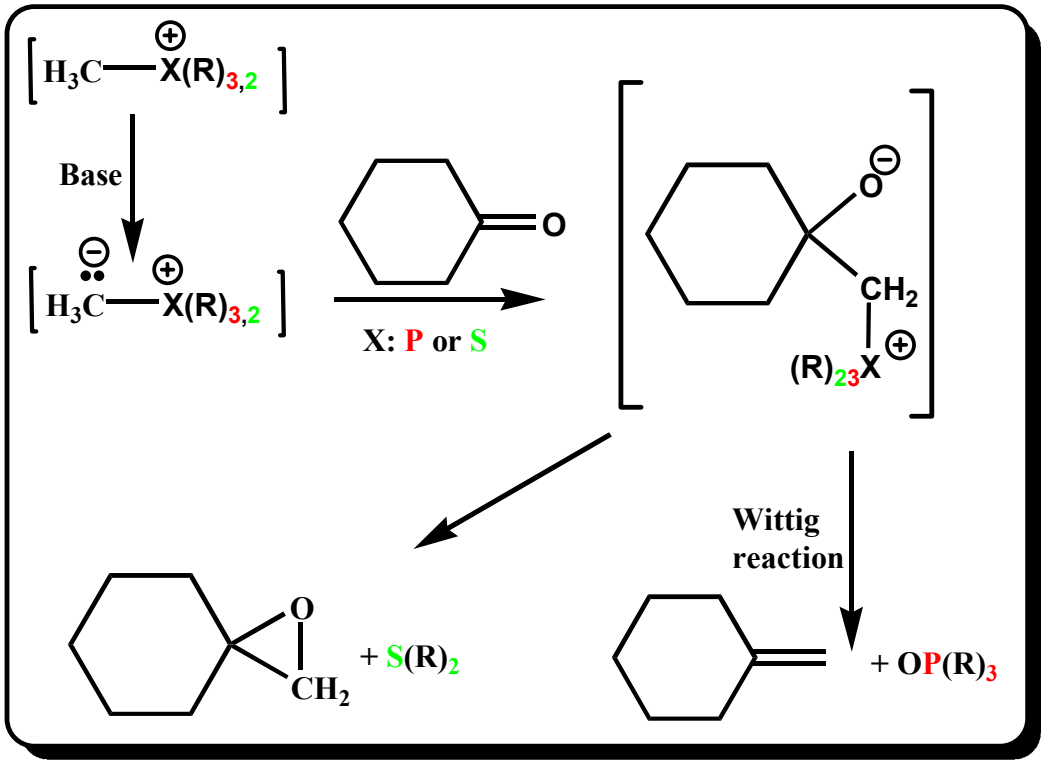


Figure 4. Reaction between a ketone and a phosphonium ylide as well as sulfonium ylide.

-nism which occurs between the cyclohexanone and the phosphonium ylide is based on the nucleophilic attack of the carbanion to the carbon of the carbonyl group. This first step generates a negatively charged oxygen that attacks the positively charged phosphorus giving rise to a four membered ring. The following decomposition of the four membered ring allows the title products, methylene-cyclohexane and trialkylphosphine oxide. On the other hand, reaction between the cyclohexanone and the sulfonium ylide is

initiated by the manner analogous to that of the Wittig reaction[5]. The two reactions diverge at the second step. In the case of sulfur, the oxyanion nucleophilic attack is to the carbon rather than the sulfur, forming correspondingly the 1-Oxa-spiro[2.5]octane. In spite of the greater ability of sulfur to stabilize an adjacent carbanion by valence shell expansion, sulfur seems less suitable toward the bond formation of a higher covalency intermediate. It is interesting to note that the methyl sulfide is known to be an excellent leaving group which tends to favor epoxide formation over olefin formation[5'].

1.3 Ammonium Ylides

1.3.1 Ammonium ylide stability

As mentioned above, phosphonium and sulfonium groups emphasized the acidity of α-hydrogen atoms. In this case of ylides, the strength of this effect has been attributed to the stabilization of the resulting carbanion by overlap with the vacant, low energy 3d-orbital of the onium atom.

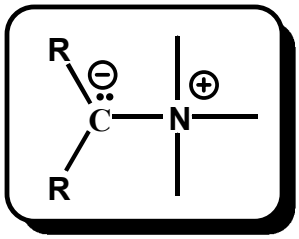


Figure 5. Ammonium ylides molecular structure.

Being a first row element with filled 2s-, and 2p-orbitals, the nitrogen atom has the next available empty orbital located at the 3s-orbital, which is at a much higher energy level relative to the corresponding vacant 3d-orbitals of phosphorus and sulfur

atoms. Therefore, nitrogen molecular orbital system is less available for overlap with potential stabilization of a carbanion, as shown on the molecular system **Figure 5**. Therefore, the ammonium group[6] and the adjacent carbanion ylide system are mainly stabilized by electrostatic interactions between the opposite charges. It must be pointed out that the absence of other than electrostatic stabilization by positively charged nitrogen has not been rigorously proven. Nevertheless, the larger acidifying ability of the lower row elements usually are interpreted as being due to shell expansion and assumes the absence of such stabilization for nitrogen. Accordingly, nitrogen ylides would be expected to be more difficult to prepare and, perhaps, to be less stable once prepared.

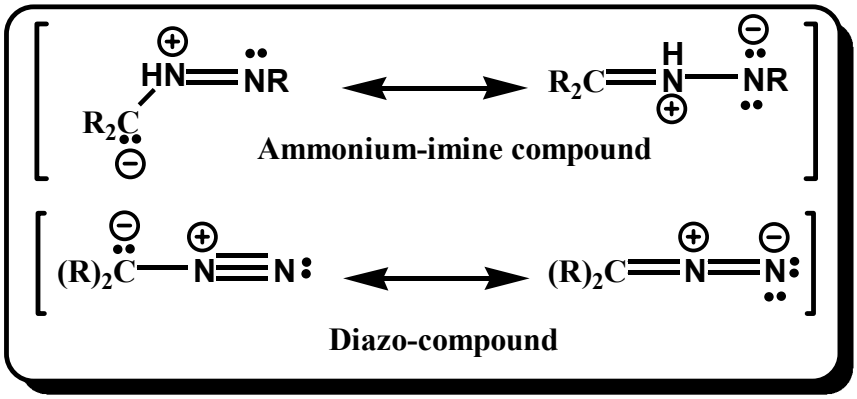


Figure 6. Ammonium-imine and diazo ylides molecular structure.

Nitrogen ylide families[6'] encompass many isoelectronic substances, such as ammonium-imine compounds, or diazo-compounds (**Figure 6**). Those systems exhibit very similar physical and chemical properties relative to conventional nitrogen ylides. Sometimes stable enough to be isolated, the substituents (**R**) attached to the carbon of (**Figure 6**) compounds are inevitably those which could afford maximum stabilization of a carbanion. Therefore, species with electro-donating groups in α-position of the

carbanion have been extensively isolated. Similar to nitrogen ylides, ammonium-imine as well as diazo-compounds allow reactions from the active carbanion site such as alkylation, acylation, direct attack toward electrophiles, or even attack toward unsaturated groups.

1.4 Pyridinium Ylides

Pyridinium ylides represent an alternative nitrogen derivative ylide that allows much more stabilization of the carbanion relative to the ammonium ylide. First discovered by Krohnke[7] in 1935, the carbanion is stabilized by resonance with the pyridinium ring (**Figure 6**). These ylides undergo normal carbonionic reactions, such as alkylation and acylation. It must be pointed out that in order for the ylide to be capable of isolation, in other words, to enhance stabilization, at least one of the groups R or R' (**Figure 6**), must be capable of stabilizing the carbanion by resonance.

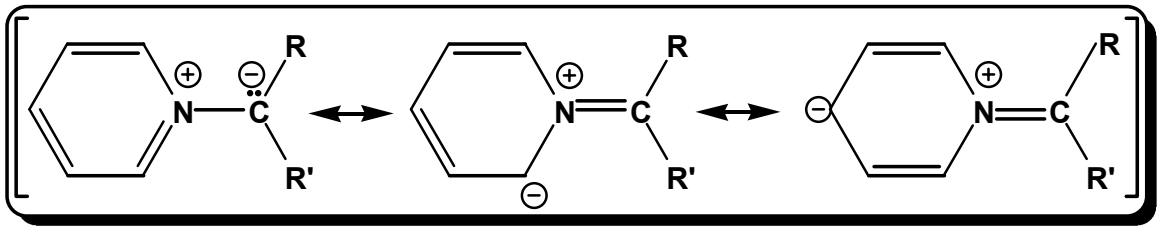


Figure 7. Carbanion stabilization by resonance with the pyridinium ring.

Therefore, electron-withdrawing groups such as aldehyde, ketone, ester, cyano, and so on attached to the carbanion exhibit better stabilization (**Figure 7**).

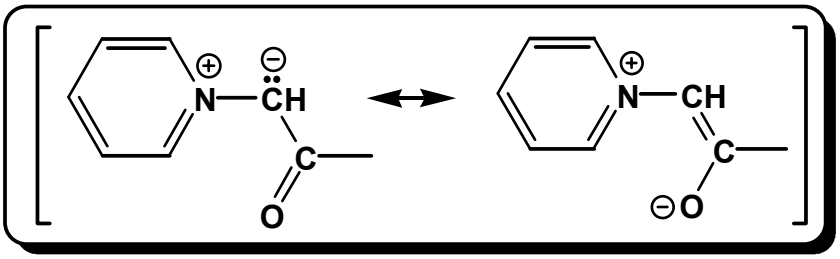


Figure 8. Carbanion stabilization by resonance with electron-withdrawing group.

Keeping in mind the enhanced stability of pyridinium ylides by resonance stabilization of the electron-withdrawing groups in α-position of the carbanion, Thomas Kappe and Co-workers[8-10] synthesized and isolated pyridinium ylides of barbituric acid (**Figure 8.**). The use of barbituric acids as anionic moieties allows the carbanion to be stabilized by both carbonyl groups in α-position. Thus, the heterocyclic ylides produced were quantitative relative to an enhanced stabilization composed of electrostatic and resonance stabilization.

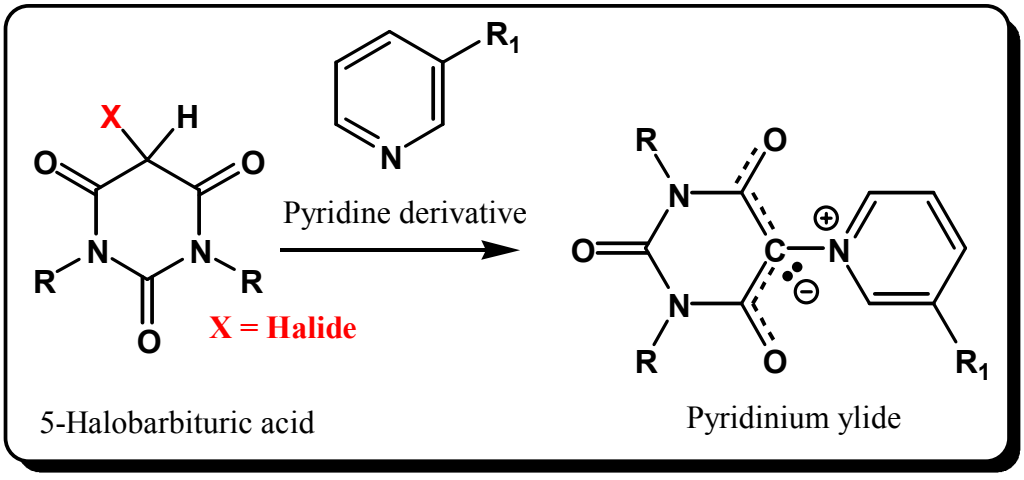


Figure 9. Reaction of 5-halobarbituric acid and pyridine derivatives.

Polarity of the solvent is critical for the formation of these ylides. Two most commonly used solvents are DMF and ethanol. Reaction mixture was refluxed for a maximum of 30 minutes and product was isolated by filtration of the crystalline product. Recristallization in methanol gave the purified targeted products. Isolated yields of those pyridinium ylides are quantitative. The uses of barbituric acid as anionic moieties allow some valuable nitrogen ylides relative to purity and stability. Using the same idea, Youssif[11] and Co-worker synthesized nitrogen ylides starting from barbituric acid and quinoline N-oxide as the cationic moiety in 1981.

2. PART I. DIAMINOCARBONIUM BARBITURIC ACID YLIDES

2.1 Introduction

The derivatives of barbituric acid have a special place in pharmaceutical chemistry. Their biological activities range from classical applications in medical treatment as hypnotic, sedative, and anesthetic[12] drugs to more recent reports indicating that they have application in anti-tumor[13], and anti-osteoporosis[14] treatments.

Physico-chemical properties of barbituric acid is based on a strong acidity (pKa = 4.01 in water). It is partially soluble in solvents such as water and methanol in which barbituric acid continue to have strong acidic properties[21]. One of the interesting aspects of barbituric acid is an "active" methylene group which can take part in condensation reactions with aldehydes or ketones[22] that do not contain an α-hydrogen.

It was previously pointed up out some simple nitrophenylhydrazones containing aromatic ketones (Compound **1**, **Figure 9.**) exhibit strong anticancer activity.[15] In addition, it was also determined that these compounds exhibit immuno-modulating[16] and strong molecular binding capabilities.[17] Therefore, it is speculated that the anticancer activity of **1** might be a result of the immuno-modulating capabilities of these compounds.[18] There are also some literature that highlights both the anticancer[19] and immuno-modulating[20] capabilities of barbituric acid derivatives. This has led our research

toward the development of new barbituric acid derivatives **2** as anticancer drugs that act as immuno-modulating agents[23].

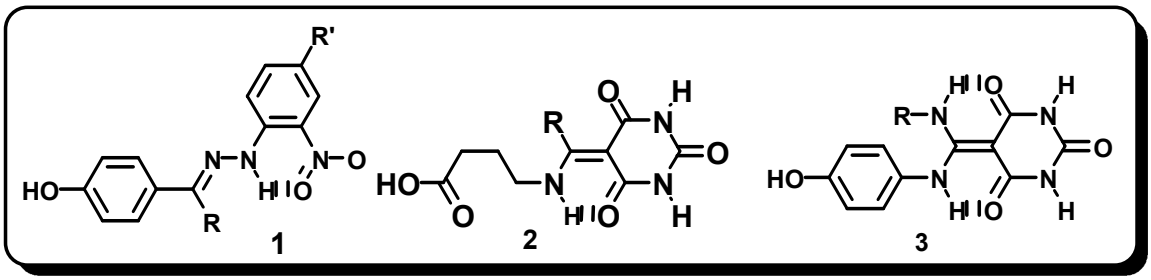


Figure 10. Structures of known anticancer compounds **1** and **2** and our general synthetic target **3**.

By close comparison of the structural properties of the biologically active compounds that have been prepared and tested in our laboratories, we have extended our search for anticancer compounds to a new family of barbituric acid derivatives that have the structural properties of compound **3** (**Figure 9**). If biological evaluation of the structural isomers of **3** appears to be successful, then reliable synthetic procedures for the preparation of these isomers will be developed. These procedures should provide the synthesis of large quantities of pure material, and the application of a common synthetic procedure for the preparation of several structural derivatives of isomer **3**.

Examining the structural characteristics of our target molecule (Compound **3**, **Figure 10.**), it is clear that **DABA** contains two moieties, urea and barbituric acid. Those readily available starting reagents[24] can be condensed together by elimination of one water molecule. Although condensation reactions between carbonyl compounds and barbituric acid are well documented, the reaction is mostly successful with aromatic aldehydes and with some activated ketones[25]. In order to perform urea-barbituric acid

condensation, urea should be activated from its transformation into a more reactive intermediate, such as carbodiimide (**Figure 10**). Then, **DABA** derivatives can be prepared by barbituric acid addition to carbodiimides. To the best of our knowledge there is no available literature procedure for the preparation of **DABA** derivatives from urea (carbodiimides)[26] and barbituric acid.

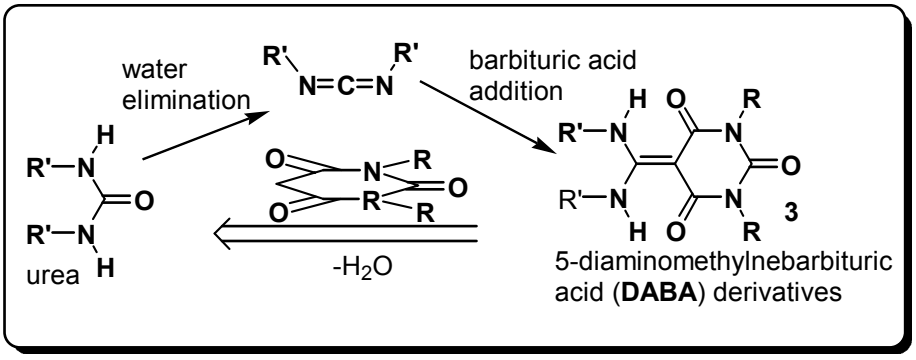


Figure 11. Transformation of barbituric acid and urea derivatives into **DABA** derivatives.

However there are some reports that suggest that this synthetic approach might be successful. It was demonstrated that compounds with active methylene groups, such as diethyl malonate can add to carbodiimides[27].This condensation reaction was carried out at high temperature with diphenyl ether as the reaction media. In many chemical reactions, barbituric acid is considered to be a compound with an active methylene group. By mixing barbituric acid and 1,3-dicyclohexylcarbodiimide together in THF in presence of pyridine, immediately the color of the reaction mixture changes to fluorescent purple. In fact, DCC combined with pyridine has been used for the analytical detection of barbituric acid, [28]but the products for this reaction have not been isolated[29].

2.2 Results and Discussion

In our initial experiments, we demonstrated that in THF the addition of barbituric acid and DCC requires a long time to be completed (several weeks at room temperature).[30] Additionally, besides the major product of this reaction, the 1,3-dicyclohexylurea byproduct of water addition to DCC can be obtained. This does not match with the synthetic procedure that we are seeking in our preparation of the large number of structural isomers for biological applications. Therefore, we have carefully explored reaction conditions for the barbituric acid addition to carbodiimides through NMR experiments.

Experiments are performed in aprotic solvents such as tetrahydrofuran, dioxane, benzene, toluene, dimethylformamide, and dimethyl sulfoxide. The solubility of barbituric acid in some of these solvents is very low. The optimized experimental data which can be applied to large scale (100 g) preparations of target compound **3** are obtained in DMSO as the solvent of reaction. Although reaction conditions for every listed compound in this paper were optimized through NMR following experiments, only our results for the barbituric acid and 1,3-dimethylbarbituric acid addition to 1,3-di(4-methylphenyl)carbodiimide will be discussed. The addition of barbituric acid is a very slow process; when water is present in the reaction media, the water addition to carbodiimide becomes the dominant reaction, as shown in the **Figure 11** with the NMR reaction following experiment of the barbituric acid addition to di(4-methylphenyl)carbodiimide at room temperature. The use of 10 equivalents of barbituric acid excess ensured that large quantities of water were added into the reaction media. All starting material was practically consumed after 24 hours at room temperature and 1,3-

di(4-methylphenyl)urea was formed (**Figure 11**). We believe that this urea derivative directly forms a molecular complex with the surrounding barbituric acid, which is evident by the presence of the NH singlet of the barbituric acid moiety in the complex at 10.15 ppm. The same NMR pattern is obtained for the DMSO solution of barbituric acid and 1,3-di(4-methylphenyl)urea. There is only a small amount of the desirable product **4**. With increase of the temperature, the ratio between the product and the urea derivative increases (**Figure 11**). It seems that the best reaction temperature is 150˚C, from which the reaction is completed after 15 minutes and more than 95% of the target product **4** is formed.

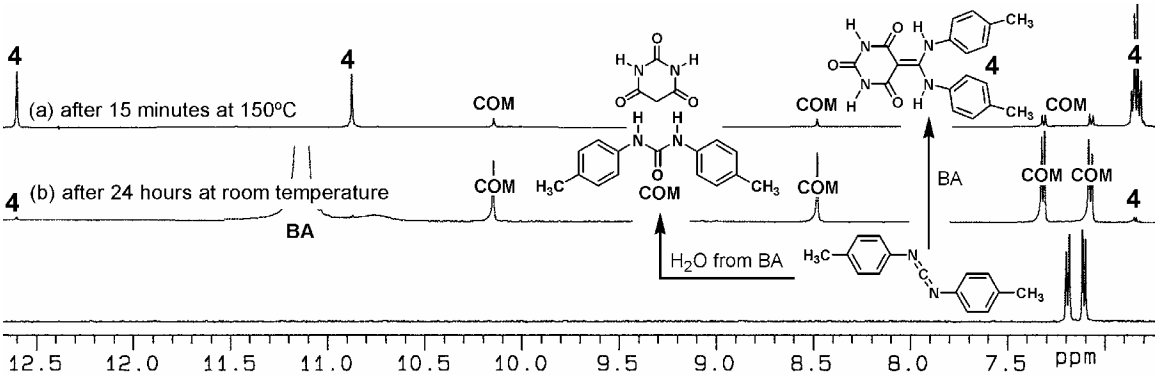


Figure 12. The ^{1}H-NMR reaction following of barbituric acid (10 mM) addition to 1,3-di(4-methylphenyl)carbodiimide (1 mM) in DMSO-d_6 (1 ml)

Similar results were observed when the other barbituric acid derivatives were added to di(4-methylphenyl)carbodiimide. This is demonstrated by the methyl portion of the NMR in the 1,3-dimethylbarbituric acid addition to 1,3-di(4-methylphenyl)carbodiimide (**Figure 12**). The water concentration here is substantially lower than in the previous experiment (bulk of the water in the reaction media is associated with barbituric acid) and the desired product **5** is formed more extensively.

The addition of the barbituric acid is very slow at room temperature and it requires nine days for both reactants to be consumed (**Figure 12**). In 1 mM/1mL concentration almost equimolar ratio of product **5** and the molecular complex was formed (**Figure 12**). If the reaction was performed at 150ºC for 15 minutes then the major product of the reaction (95% conversion) is the condensed product **5**.

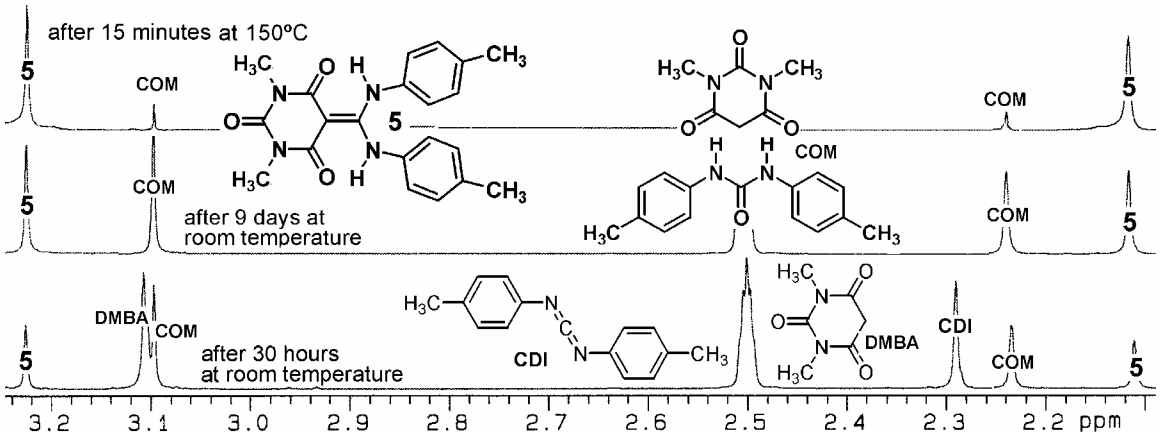


Figure 13. The methyl portion of the ^{1}H-NMR following for 1,3-dimethylbarbituric acid (1 mM) addition to 1,3-di(4-methylphenyl)carbodiimide (1 mM) in DMSO-d_6 (1 ml).

From these experiments, it is obvious that our target compounds can be prepared at elevated temperatures (150ºC) in a very short reaction period (15 minutes). Quantitative yields of the condensation products can also be obtained if the reaction is performed in other inert solvents, such as tetrahydrofuran at room temperature. Tetrahydrofuran solution of barbituric acid should be dried over molecular sieves for a few days to eliminate the presence of water that is usually contained in barbituric acid. Into this dried solution, the corresponding carbodiimide should be added and the reaction mixture should be kept in a closed container at room temperature for fourteen days. Solvent was evaporated and the remaining residue was crystallized from methanol,

yielding the pure target compounds **4-12** in 85-95% yield. The low solubility of barbituric acid derivatives in tetrahydrofuran limits this procedure to be practical for the preparation of small quantities of 5-diaminomethylenebarbiturates. For large-scale preparation DMSO is much more suitable as reaction solvent. Isolated yields and applied methods for the preparation of 5-diaminomethylenebarbiturates **4-12** are listed in **Table 1**.

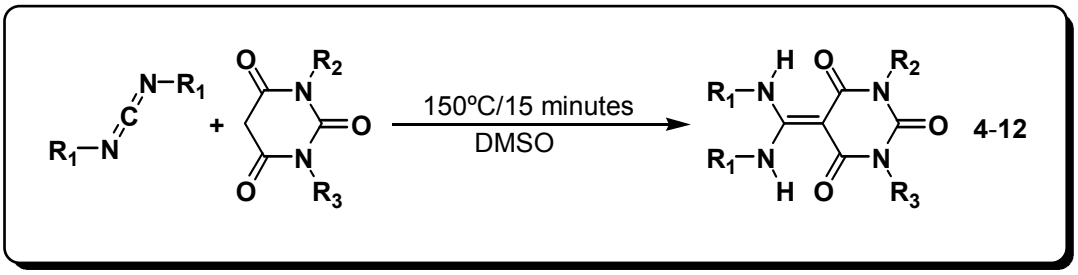


Table 1. Isolated Yields of 5-diaminomethylenebarbiturates **4-12**

	Compound	Method	R_1	R_2	R_3	Yield (%)
1	**4**	A	4-$CH_3C_6H_4$	H	H	89%
2	**5**	B	4-$CH_3C_6H_4$	CH_3	CH_3	90%
3	**6**	A	4-$CH_3C_6H_4$	C_6H_5	H	89%
4	**7**	C	$(CH_3)_2CH$	H	H	83%
5	**7**	D	$(CH_3)_2CH$	H	H	86%
6	**8**	C	$(CH_3)_2CH$	CH_3	CH_3	87%
7	**8**	D	$(CH_3)_2CH$	CH_3	CH_3	85%
8	**9**	C	$(CH_3)_2CH$	C_6H_5	H	92%
9	**9**	D	$(CH_3)_2CH$	C_6H_5	H	87%
10	**10**	E	C_6H_{11}	H	H	89%
11	**11**	B	C_6H_{11}	CH_3	CH_3	95%
12	**12**	B	C_6H_{11}	C_6H_5	H	93%

To confirm the structural properties of the prepared target barbituric acid derivatives, compound **11** was selected for X-ray structural studies. Our spectroscopic data for 5-diaminomethylidenebarbiturates are in full agreement with the X-ray determined structure of **11** (**Figure 14**). It is interesting to mention that the C(7)-C(8) bond between urea and the barbituric acid moiety has only partial double bond character.

The compound can be better described as an ylide with a positive charge located on the urea carbon and a negative charge on the barbituric acid moiety. This charge separation is perfectly demonstrated with strong [=O---HN] hydrogen bonding and a very high chemical shift for the urea NH hydrogen (**Figure 14**).

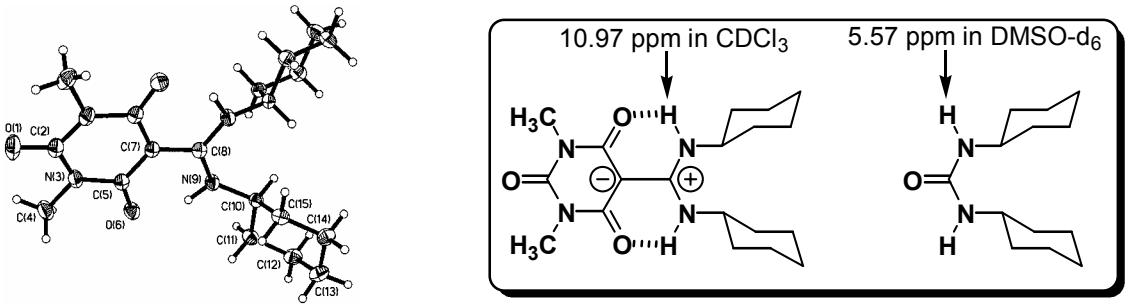


Figure 14. ORTEP drawing of X-ray determined structure of **11** and its ylide structure (performed by Dr Stevens)

2.3 Conclusions

It can be concluded that through the careful NMR experiment, it was possible to develop a general synthetic procedure for the preparation of large quantities of 5-diaminomethylenebarbiturates from substituted carbodiimides (urea) and barbituric acid. Preparation of a series of structural isomers of these compounds is now possible. It was also demonstrated that strong electrostatic interactions between these two moieties (urea and barbituric acid) exist. These interactions are responsible for strong charge separation through the molecule that is characteristic of ylide-like structural properties.

1. Part I reprinted from Tetrahedron lett., Vol. 59; Jursic, B. S.; Douelle, F.; Stevens, E. D. Preparation of 5-Diaminomethylenebarbiturate by Barbituric Acid Addition to Carbodiimide, Pages 3427-3432, Copyright (2003), with permission of Elsevier

3. PART II. PYRIDINIUM METHYLENE BARBITURIC ACID YLIDES

3.1 Introduction

Our interest was focused on the design of pyridinium ylide containing a carbon unit between the polarized fragment (**Compound 13**, **Figure 15**). Compound **13** can be divided into three distinct fragments such as a negative and positive moiety connected to a single neutral carbon unit. Although no mechanistic studies have been performed for this reaction, it is thought that the carbon at the five position of the barbituric acid molecule generate a nucleophilic attack to the electropositive carbon of the paraformaldehyde. Via condensation, a resulting α,β-unsaturated carbonyl is intermediately formed and is typically seen as a good "Michael acceptor". The unsaturated β carbon atom is then exposed to nucleophilic attack from the nitrogen heteroatom of the pyridine ring. It is expected that the targeted compounds **13-17** (**Figure 14)** might exhibit a limited stability based on the carbon unit inserted between the dipole fragments. Although the carbanion might be reasonably resonance stabilized by the carbonyl groups in the α - position, and the nitronium moiety resonance stabilized around the aromatic ring, the electrostatic interactions between the opposite charges are significantly depleted. For instance, it is believed that targeted compounds are acid as well as heat sensitive. Therefore, prior to these experiments, gentle conditions were required for the successful completion of this reaction.

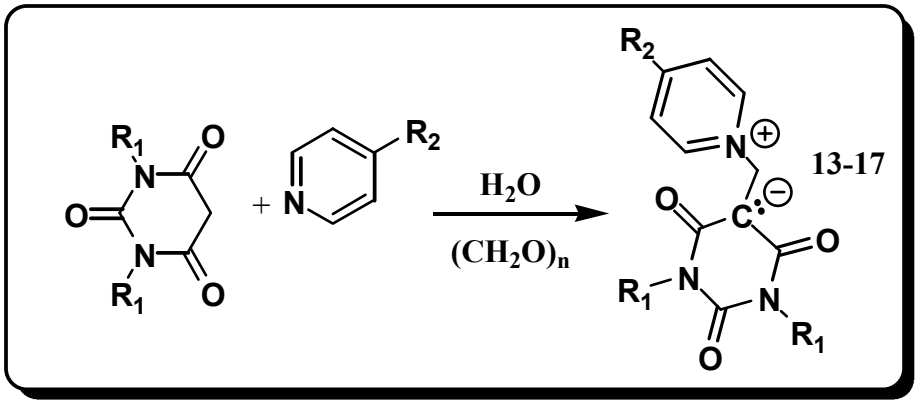


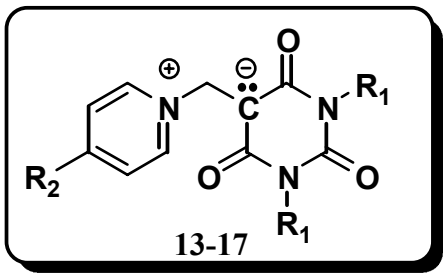
Figure 15. Reaction between barbituric acid derivatives, pyridine derivatives and paraformaldehyde

3.2 Results and discussion

In our initial experiments protic polar solvents such as propanol were used to perform the reaction shown in **Figure 15.** The concentration of one third of the reaction mixture after a reflux of one hour precipitate the major product **13** (**Table 2**). After a cold propanol wash, the resulting pure crystals were characterized by ^{1}H–NMR. We believed that the use of solvent with lower boiling point would allow easier major product precipitation. A preliminary reflux of 4-dimethyl-aminopyrimidine with 1,3-dimethylbarbituric acid was fully dissolved in water after thirty minutes. After an addition of an excess of paraformaldehyde (3 equivalents) into the clear reaction mixture, mixture was refluxed again over forty five minutes.

The reaction equilibrium was reached from which the ratio between compound **13** and the starting materials was the highest. The reaction mixture was left at room temperature during two hours affording the resulting 5-ylide-pyridinium-methyl barbituric acid derivatives **13** and **14** to precipitate with quantitative yields (**Table 2-Procedure F**). Using the same procedure, 4-aminopyridine was utilized for the design of compound **15**.

The resulting ^{1}H NMR of the solid which precipitated once the reaction mixture was allowed to cool down showed a mixture of products.



13-17

Table 2. Isolated yields of some 5-ylide-pyridinium-methyl barbituric acid derivatives

Compound	Procedure	R_1	R_2	Yield (%)
13	F	CH_3	$N(CH_3)_2$	90.0
14	F	H	$N(CH_3)_2$	93.5
15	F	CH_3	NH_2	X
16	F	CH_3	OCH_3	X
17	F	CH_3	Cl	X

X: Compounds were demonstrated by ^{1}H NMR but were not isolated.

It is thought that a competition between the nitrogen heteroatoms and the para primary amine group of the pyridine ring occurred for the nucleophilic attack of the unsaturated β carbon atom. Acid sensitivity of targeted compound **15** did not permit efficient separation techniques using silica gel flash chromatography due to the fact that silica gel initiated the decomposition of the compound. Thermal sensitivity of the targeted compound **15** combined with its poor solubility at room temperature in most traditional solvents led to unsatisfactory isolation by crystallization techniques.

Using the same **procedure F**, 4-methoxypyridine was employed to design compound **16**. Close NMR spectroscopic monitoring was applied to the refluxed reaction mixture after the addition of the paraformaldehyde. By ^{1}H NMR spectroscopy, a clear

ratio of 1/1 equilibrium between the starting materials and the targeted compound **16** was observed over an extended period of time (1 week). More harsh experimental conditions were applied to the reaction, such as the use of more polar solvent (dimethylsulfoxide) at 160ºC. The product formed was rapidly decomposed driving the reaction equilibrium back into starting materials. The reaction in a NMR tube was attempted using three times more concentrated starting materials relative to the starting materials quantities and the volume of water used for the procedure F. It is thought that those conditions would drive the reaction equilibrium toward the formation of the product compound **16.** Instead, a similar ratio of starting materials and product were observed. These results were unexpected because the electron-donating effect of the methoxy group in the para position of the pyridine ring should traditionally enhance the electron-density of the aromatic system, and favoring the nucleophilic capacity of nitrogen heteroatom.

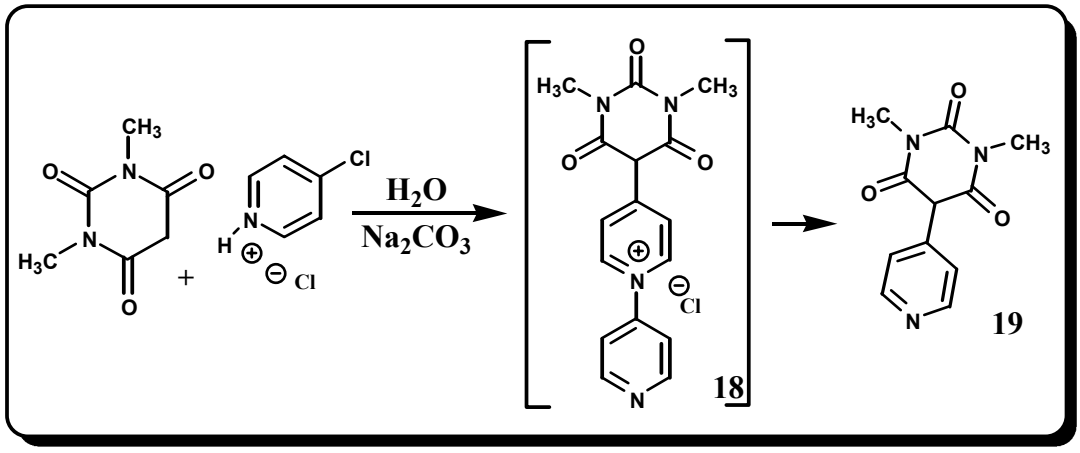


Figure 16. Reaction between barbituric acid derivatives, and 4-chloropyridine hydrochloride

Prior to the reaction, the 4-chloropyridinium hydrochloride salt was neutralized by addition of an excess of sodium carbonate in aqueous solution. Once the carbon

dioxide release in solution was no longer observed, 1,3-dimethylbarbituric acid was added to the aqueous media. The next steps carefully followed the **procedure F**. Close NMR spectroscopic monitoring of the refluxed reaction mixture after the addition of paraformaldehyde showed the formation of the polymeric intermediate **18** (**Figure 15**) which under further 1,3-dimethylbarbituric acid nucleophilic attack decomposed into compound **19**. Clearly by spectroscopic observations, the paraformaldehyde molecule did not take place in the reaction. Instead, good leaving group capability of chlorine in the para position of the pyridine ring led to a selective nucleophilic substitution in the para position of the pyridine ring. In order to stabilize the intermediate **19,** two equivalents of 4-chloropyridine hydrochloride were refluxed with one equivalent of 1,3-dimethylbarbituric acid in water with two equivalents of sodium bicarbonate. Again, the major product isolated was the monomeric moiety **19**.

Previous research performed by our research group[31] gave the isolation of 5-ylidene barbituric acid derivated in almost quantitative yield (compound **20**, **Figure 16**). The reaction was based on the condensation of aromatic, and α,β-conjugated aromatic aldehydes with barbituric acid in methanol solution in the absence of acid or base as a catalyst. Our idea (**Figure 16**) was to use these previously synthesized 5-ylidene barbituric acid derivatives as starting materials, rather than the *in-situ* generation of the condensation products, as previously attempted with barbituric acid derivatives and paraformaldehyde (**Figure 14**). Thus, the nucleophilic attack of pyridine derivative to the unsaturated β carbon from the corresponding α,β-unsaturated carbonyl might be selectively induced.

Our first goal was to produce and stabilize the corresponding compound **20'** under more gentle experimental conditions. Secondly, 5-ylidene barbituric acid derivatives (**20**) with substituent R_2 different than hydrogen would allow the formation of a chiral center.

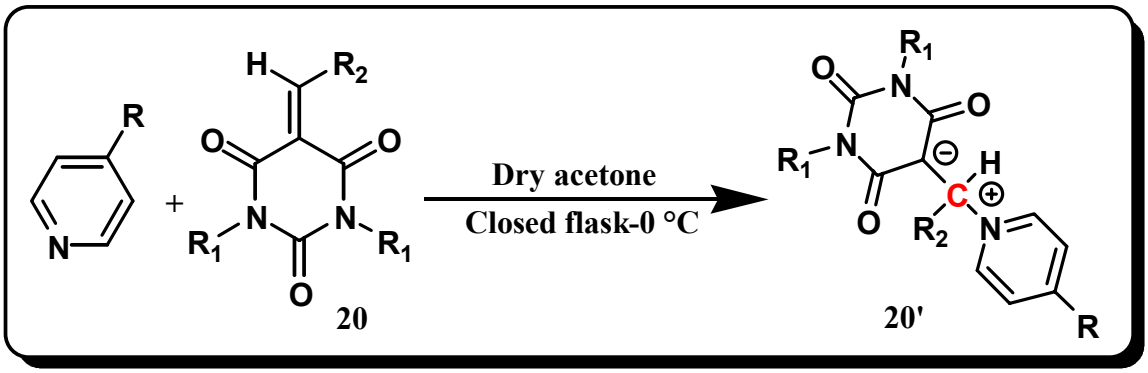


Figure 17. Synthesis of 5-ylide-pyridinium-chiralmethyl-barbituric acid derivatives from Pyridine derivatives and 5-ylidene barbituric acid derivatives

In our initial experiment, we demonstrated that in methanol at room temperature, 4-dimethylaminopyridine was added to the 5-benzylidene-1,3-dimethyl-pyrimidine-2,4,6-trione. Forty five minutes reaction time at room temperature was required to form the corresponding product **20'** (**Figure 17**) in solution. However, during the course of this time, decomposition of the 5-ylidene barbituric acid derivatives occurred, giving the benzaldehyde as well as dimethylbarbituric acid back in solution. The reaction was followed by ^{1}H-NMR using less polar solvents such as THF at room temperature. These results essentially showed decomposition of the 5-Benzylidene-1,3-dimethyl-pyrimidine-2,4,6-trione as well. It is believed that 5-ylidene barbituric acid derivatives are water sensitive and then decomposed via hydrolysis. Therefore the tiny amount of water trapped in methanol or THF seemed to be a sufficient amount to induce decomposition of the corresponding ylide.

The optimized experimental reaction conditions were carried out in dry acetone at 0ºC in a closed flask (**Procedure G**). The low solubility of **21** forced us to enhance the volume of dry acetone (200mL for 244mg of **21**). To overcome any decomposition of the 5-benzylidene-1,3-dimethyl-pyrimidine-2,4,6-trione (General structure **20**), it was necessary to do the reaction work-up at 0ºC.

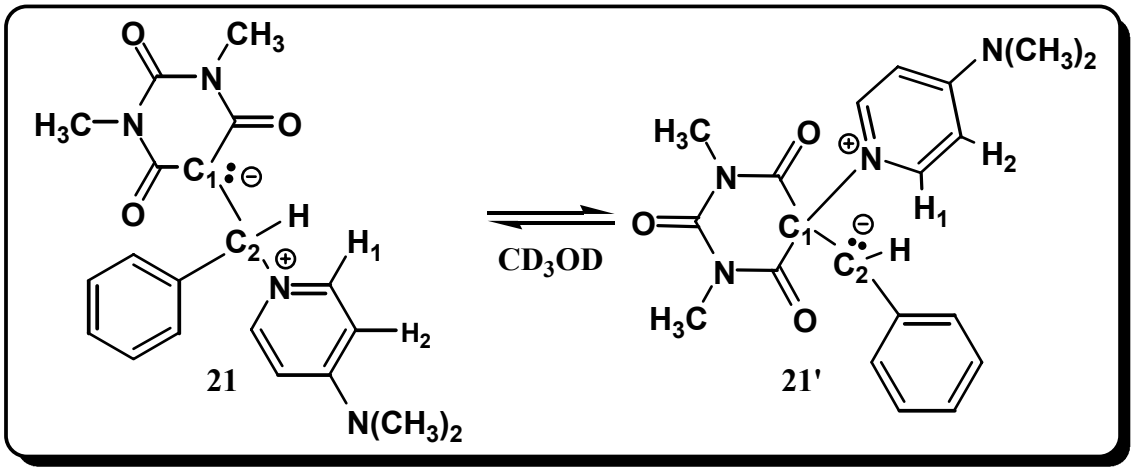


Figure 18. Equilibrium between C_1-pyridinium ylide and C_2-pyridinium ylide in cd_3cod at room temperature.

The ^{1}H-NMR of compound **21** in methanol (CD_3OD) is given in **Figure 18**. This shows equilibrium between the C_1-pyridinium ylide and the C_2-pyridinium ylide with **21**/**21'** ratio of 67/33. Structure **21** relative to **21'** (**Figure 17**) are distinguishable from ^{1}H-NMR such that the singlet for the hydrogen at the C_2 position (**21**) has a chemical shift of 6.8 ppm, whereas the singlet for the hydrogen at the C_2 position (**21'**) is shielded at 5.7 ppm due to the higher electron density nature of the carbanion at C_2. The doublet (d, $2H_1$) from the 4-dimethylaminopyridine moiety (**21**) is more deshielded compared to the doublet (d, $2H_1$) from the 4-dimethylaminopyridine moiety (**21'**) due to the more pronounced inductive effect of the dimethyl barbituric acid moiety. An opposite trend can

be observed for the doublet (d, $2H_2$) from the 4-dimethylaminopyridine moiety (**21**) relative to (**21'**) such that dimethylamino group in the para position of pyridine rings effects more strongly the doublet (d, $2H_2$) (**21**) compared to (**21'**).

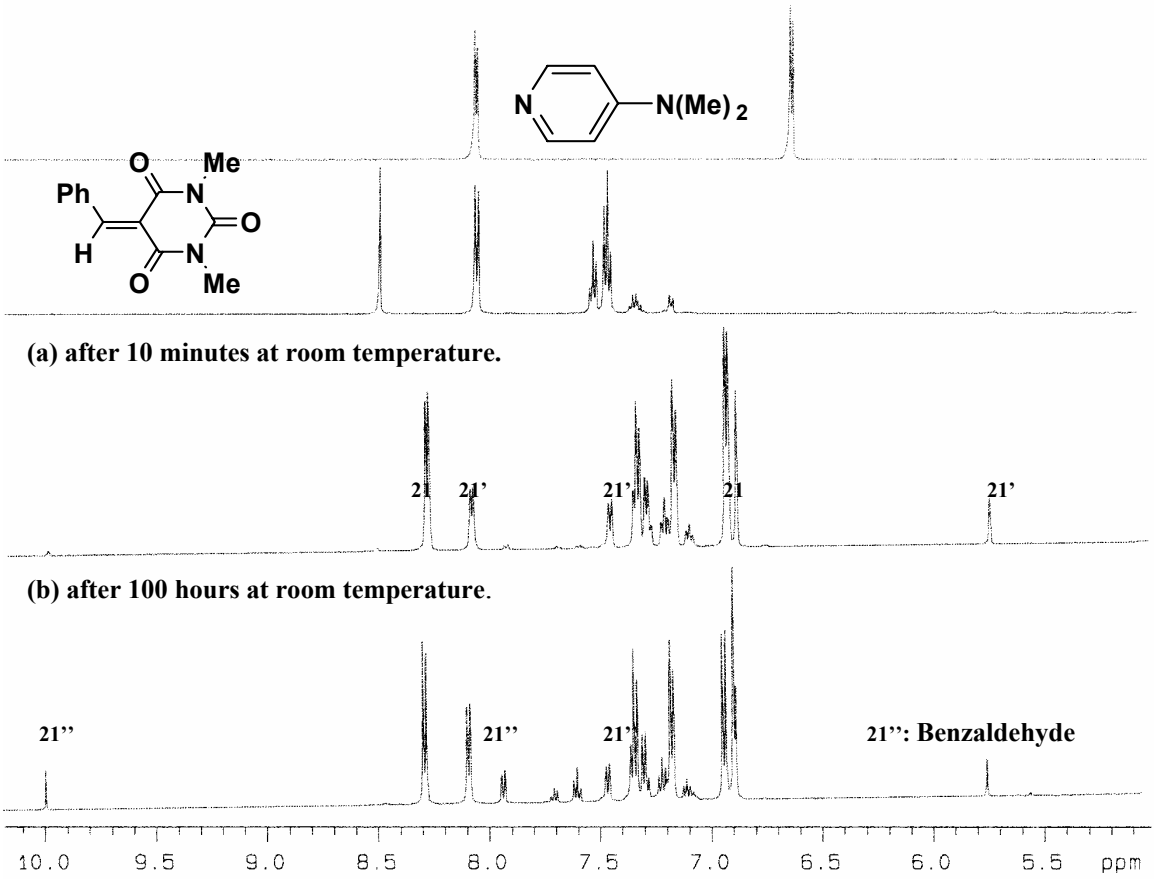


Figure 19. ^{1}H-NMR spectroscopic monitoring of **21-21'** in CD_3OD at room temperature.

We hoped that by dissolving **21-21'** mixture in a suitable solvent at room temperature for a certain time, equilibrium could be driven to one conformation over the other (**Figure 17**). DMSO-d_6 initiated the decomposition behavior right after the dissolution of the mixture. Chloroform ($CDCl_3$) was not polar enough to dissolve the mixture. CD_3OH seemed to be the most suitable solvent such that the decomposition behavior was not initiated before one hour. The ^{1}H-NMR recorded after 100 hours showed **21/21'/benzaldehyde** ratio of 57/32/11. Therefore, it is interesting to note that

mainly **21** decomposed and released benzaldehyde as well as dimethylbarbituric acid into solution, whereas **21'** seemed to remains stable. The ^{1}H-NMR recorded after 200 hours did not show any change on the **21/21'/benzaldehyde** ratio. Having stored the CD_3OD solution at 0ºC did not dramatically alter **21/21'** ratio and decomposition still occurred.

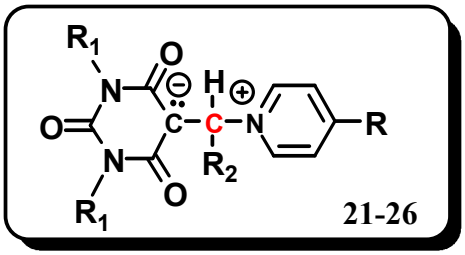


Table 3. Attempts of preparation of 5-ylide-pyridinium-chiralmethyl barbituric acid derivatives.

Product	Procedure	R	R1	R2	Yield (%)
21	G	$N(CH_3)_2$	CH_3	Phenyl	93
22	G	$N(CH_3)_2$	H	Phenyl	Reversible reaction
23	G	$N(CH_3)_2$	CH_3	Naphtalene	Reversible reaction
24	G	NH_2	CH_3	Phenyl	By-product
25	G	$N(CH_3)_2$	CH_3	p-$O(CH_3)$-phenyl	No reaction
26	G	$N(CH_3)_2$	CH_3	p-$N(CH_3)_2$-phenyl	No reaction

Furthermore, we explored the design of 5-ylide-pyridinium-chiralmethyl-barbituric acid derivatives **(Compounds 22-26, Table 3)** in order to verify the versatility of the procedure G. The first attempt was to change the 5-benzylidene-1,3-dimethyl-pyrimidine-2,4,6-trione for 5-benzylidene-pyrimidine-2,4,6-trione to yield the product **22**. Surprisingly, ^{1}H-NMR monitoring pointed out that the reaction did not go to completion even with extended reaction times. The precipitated solution (dry acetone-0ºC) was composed of equilibrium between starting materials and product **22**. The reaction carried

out at room temperature partially decomposed 5-benzylidene-pyrimidine-2,4,6-trione (general structure **20**). The reaction progress of the targeted compound (**23**) showed the same trend as compound (**22**).

The reaction between para-aminopyridine and 5-benzylidene-1,3-dimethyl-pyrimidine-2,4,6-trione demonstrated a random nucleophilic attack of either the nitrogen heteroatom of the pyridine ring or the para-primary amino-group. Again product **24** could not be isolated.

As expected, product **25** and **26** did not form. Electro-donating groups in para position of the phenyl ring inhibit greatly the nucleophilic attack of the β carbon from the corresponding α,β-unsaturated carbonyl. Therefore, no reaction occurred either at 0ºC or room temperature. Instead, 5-ylidene barbituric acid derivatives started decomposing after 5 hours under reflux in dry acetone.

3.3 Conclusions

We demonstrated that 4-dimethylamino-1-(2,4,6-trioxo-hexahydro-pyrimidin-5-ylide-methyl)-pyridinium (**14**), and the corresponding 1,3-dimethylbarbituric acid derivative (**13**) were successfully prepared in quantitative yield. Conversely, the corresponding derivatives with primary amine group in R_2 position (**15**), is nucleophilic enough to compete with the nitrogen heteroatom of the pyridine ring leading to a mixture of products not isolatable. The derivative with a methoxy group in R_2 position (**16**), surprisingly did not form. The electron-donating group in the para position of the pyridine ring should traditionally enhance the electron-density of the aromatic system. The good leaving group capability of the chlorine group in R_2 position of the pyridine

ring did not allow the formation of the 5-ylide-pyridinium-methyl barbituric acid derivatives expected (**17**); instead the selective nucleophilic substitution of the chlorine occurred yielding intermediately the dimeric compound **18**, followed by the stable monomeric compound **19** (**Figure 15**). Next, an alternative approach of 5-ylide-pyridinium-methyl barbituric acid derivatives design was attempted, with the point being to generate a chiral carbon unit between the polarized pyridinium ylide.

Finally, a limited general synthetic procedure was derived for the preparation of 5-ylide-pyridinium-chiralmethyl-barbituric acid derivatives. Extreme instability of derivatives under investigation uniquely afford the 4-dimethylamino-1-[(1,3-dimethyl-2,4,6-trioxo-hexahydro-pyrimidin-5-yl)-phenyl-methyl]-pyridinium derivatives (**21**) with quantitative yield.

4. EXPERIMENTAL

4.1 General

All reagents and starting materials were purchased from Aldrich chemical company and were used without further purification. Solvents were purchased from Fisher chemical company and were used without previous distillation or drying. All NMR spectra were recorded on 500 MHz Unity Varian NMR instrument with DMSO-d_6 (2.50 ppm, for hydrogen and 39.51 ppm for carbon), $CDCl_3$ (7.27 ppm for hydrogen and 77.23 ppm for carbon), and CH_3OD (3.31 and 4.87 ppm for hydrogen and 49.0 ppm for carbon) as an internal reference. Electro-spray mass spectra analysis was performed on a Micromass Quattro 2 Triple Quadropole Masspectrometer. X-ray structure determination was performed on Bruker SMART 1KCCD automated diffractometer. Crystals of compound **11** were obtained by slow crystallization from diluted methanol solution of **11**. Melting points were determined on Electrothermal 9100 melting point apparatus and they are not corrected. Elemental Analysis was performed by Microlab, Inc., Norcross, GA.

4.2 Typical Procedure A

Preparation of 5-[di(4-methylphenylamino)methylene]pyrimidine-2,4,6-trione (4). Barbituric acid (128 mg; 1 mmol), di(4-methylphenyl)carbodiimide (222 mg; 1 mmol) and dimethyl sulfoxide (1 mL) were heated at 150˚C for fifteen minutes.

Initially, the reaction mixture was a suspension that first turned to a yellow solution and then to a dark brown solution. The ^{1}H-NMR test of the reaction mixtures suggest that all starting carbodiimide was consumed and transferred into desirable product **4** (~95%) and 1,3-di(4-methylphenyl)urea (~5%). The reaction mixture was cooled to room temperature and then diluted by methanol (~100 ml) and left at room temperature overnight for the solvent to slowly evaporate to a reduced volume of ~30 ml. Formed white precipitate was separated by filtration, washed with cold methanol (3x5 ml) and dried at 110˚C for thirty minutes to give 310g (89%) pure product. M.p. 278.7ºC. ^{1}H-NMR (DMSO-d_6, 500 MHz) δ 12.61 (2H, s, NHAr), 10.88 (2H, s, NH), 6.84 (4H, d, *J*=8.0 Hz, *m*-H), 6.81 (4H, d, *J*=8.0 Hz, *o*-H), and 2.10 (6H, s, CH_3). ^{13}C-NMR (DMSO-d_6, 500 MHz) δ 167.2, 157.9 (carbonyl carbons), 149.1, 80.3 (C=C carbonyls), 134.4, 133.7, 128.9, 122.9 (aromatic carbons, and 20.3 ppm (methyl carbon). MS-ES^{+} (CH_3OH) m/z 405 (M + CH_3OH + Na, 100%)$^{+}$, 723 (2M + Na, 90%)$^{+}$. Anal. Calc. for $C_{19}H_{18}N_4O_3$ (350.14): C, 65.13; H, 5.18; N, 15.99, Found: C, 65.11; H, 5.20; N, 15.95.

4.3 Typical Procedure B

Preparation of 5-[di(4-methylphenylamino)methylene]-1,3-dimethyl-pyrimidine-2,4,6-trione (5). A mixture of 1,3-dimethylbarbituric **acid** (156 mg; 1 mmol), di(4-methylphenyl)carbodiimide (222 mg; 1 mmol) and dimethyl sulfoxide (1 ml) was heated at 150˚C for fifteen minutes. Reaction solution was left at room temperature for two hours. White crystalline product was formed. This suspension was diluted with methanol (15 ml), and solid product was separated by filtration, washed with methanol (3x5 ml) and dried at 110˚C for thirty minutes resulting in 340 mg (90%). M.p. 211.8ºC.

^{1}H-NMR ($CDCl_3$, 500 MHz) δ 12.85 (2H, s, NH), 6.75 (4H, d, J=9.0 Hz, m-H), 6.69 (4H, d, J=9.0 Hz, o-H), 3.36 (6H, s, NCH_3), and 2.12 ppm (6H, s, CH_3). ^{13}C-NMR ($CDCl_3$, 500 MHz) δ 165.7, 158.8 (carbonyl carbons), 151.0, 81.8 (C=C carbons), 135.2, 134.0, 128.1, 123.5 (aromatic carbons), 27.9 (NCH_3 carbon), and 20.8 ppm (CH_3 carbon). MS-ES$^+$ (CH_3COOH) m/z: 379 (M+1, 55%), 767 (2M+1, 25%). Anal. Calcd for $C_{21}H_{22}N_4O_3$ (378.42): C, 66.65; H, 5.86; N, 14.81 Found: C, 66.46; H, 5.90; N, 14.70.

4.4 Preparation of 5-[di(4-methylphenylamino)methylene]-1-phenylpyrimidine-2,4,6-trione (6).

Compound **6** were prepared by following procedure outlined in *typical procedure A*. Isolated yield is 89%. ^{1}H-NMR ($CDCl_3$, 500 MHz) 12.85 (2H, broad s, ArNH), 10.90 (1H, s, NH), 7.40 (2H, t, *J*=8.0), 7.35 (1H, t, *J*=8.0 Hz), 7.18 (2H, d, *J*=8.0 Hz), 6.77 (4H, d, *J*=9.0 Hz), 6.65 (4H, d, *J*=9.0 Hz), 2.15 ppm (6H, s). ^{13}C-NMR ($CDCl_3$, 500 MHz) δ 166.5, 166.3, 165.9, 165.7, 160.1, 151.0, 125.8, 135.2, 134.0, 129.8, 128.6, 128.1, 127.9, 123.5, 80.3, and 20.6 ppm. MS-ES$^+$ (CH_3OH) m/z: 449 (M+Na$^+$, 10%), 481 (M+CH_3OH+Na$^+$ 27%), 875 (2M+Na$^+$, 100). Anal. Calcd for $C_{25}H_{22}N_4O_3$ (426.17): C, 70.41; H, 5.20; N, 13.14 Found: C, 70.29; H, 5.31; N, 13.09.

4.5. 5-(Diisopropylaminomethylene)pyrimidine-2,4,6-trione (7).

This compound was prepared by applying both *typical procedure C and D* in 83 and 86% yield respectively. ^{1}H-NMR (DMSO-d_6, 400 MHz) , 10.78 (2H, s, N**H**CMe_2), 10.43 (2H, s, NH), 3.824 (2H, m, *J*=6.0 Hz, CH), 1.21 (12H, d, *J*=6.0 Hz). ^{13}C-NMR (DMSO-d_6, 400 MHz) 166.8, 160.5, 151.7, 79.3, 45.4, and 23.2 ppm. ES-

MS+ (CH_3CO_2H) d 255 (M+H+, 100%), 337 (M+CH3CO2H+Na+, 25%), 509 (2M+H+, 30%). Anal. Calcd for $C_{11}H_{18}N_4O_3$ (254.14): C, 51.96; H, 7.13; N, 22.03 Found: C, 51.88; H, 7.23; N, 21.95.

4.6. Typical Procedure C.

Preparation of 5-[di(1-methylethylamino)methylene]-1,3-dimethyl-pyrimidi--ne-2,4,6-trione (8). A tetrahydrofuran (50 ml) solution of 1,3-dimethylbarbituric acid (156 mg; 1 mmol) and diisopropylcarbodiimide (138 mg; 1.1 mmol) was stirred in an closed round bottle flask for ten days. Solvent was evaporated and the oily residue was dissolved in absolute ethanol-benzene (1:3) solution (50 ml) and the solvent was evaporated. This procedure was repeated three more times. Semi-solid residue was mixed with methanol (100 ml) and the resulting mixture was refluxed for one hour, filtered and left in an open beaker (150 ml) at room temperature for several days. Methanol was slowly evaporated at room temperature almost to dryness. Formed large glassy-like needles of the product were separated by filtration, washed with cold methanol (3x5 ml) and dried at 110ºC for two hours to give 245 mg (87%) of pure product. M.p. 169.3ºC. ^{1}H-NMR (DMSO-d_6, 500 MHz) δ 10.75 (2H, s, NH), 3.86 (2H, m, CH), 3.12 (6H, s, NCH_3), and 1.22 ppm (12H, d, *J*=6.0 Hz, $C(CH_3)_2$). ^{13}C-NMR (DMSO-d_6, 500 MHz) δ 164.1, 160.3 (carbonyl carbons), 150.4, 81.0 (C=C carbons), 45.5, 23.0 (isopropyl carbons), and 27.3 ppm (NCH_3 carbon). MS-ES$^+$ (CH_3COOH) m/z: 283 ($M+H^+$, 100%), 365 ($M+CH_3COOH + Na^+$, 18%), 565 ($2M+H^+$, 22%), 869 ($3M+Na^+$, 25%). Anal. Calcd for $C_{13}H_{22}N_4O_3$ (382.17): C, 55.30; H, 7.85; N, 19.84 Found: C, 55.28; H, 7.90; N, 19.72.

4.7. Typical Procedure D

Compound **8** was also prepared by **Method D**. Reaction was performed with same quantities of the reactants as in *typical procedure C* except dimethyl sulfoxide (1 ml) was used as solvent. Reaction mixture was heated in closed container at 150ºC for fifteen minutes and solvent was evaporated at 10^{-3} mm pressure to oily residue. This residue was crystallized in the same manner from methanol as describe in method C. The product was prepared in 85% yield.

4.8. 5-(Diisopropylaminomethylene)-1-phenylpyrimidine-2,4,6-trione(9).

Compound **9** was prepared by following *typical procedure C and D* in 92 and 87% yield respectively. ^{1}H-NMR (DMSO-d_6, 500 MHz) δ 10.75 (2H, s, NH), 2.03 (1H, s, NH), 7.45 (2H, t, *J*=7.5 Hz), 7.34 (1H, t, *J*=7.5 Hz), 7.19 (2H, d, *J*=7.5 Hz), 3.86 (2H, m, CH), and 1.22 ppm (12H, d, *J*=6.0 Hz, $C(CH_3)_2$). ^{13}C-NMR (DMSO-d_6, 500 MHz) δ 164.2, 163.7, 160.3, 150.2, 135.7 129.2 128.3 127.5, 81.0, 45.3, and 22.7 ppm. MS-ES^+ (CH_3COOH) m/z: 331 ($M+H^+$, 30%). Anal. Calcd for $C_{17}H_{22}N_4O_3$ (330.17): C, 61.80; H, 6.71; N, 16.96 Found: C, 61.72; H, 6.81; N, 16.83.

4.9 Typical Procedure E.

Preparation of 5-[di(cyclohexylamino)methylene]pyrimidine-2,4,6-trione (10). Dimethyl sulfoxide (150 ml) suspension of barbituric acid (12.8 g; 0.1 mol) and dicyclohexylcarbondimide (20.6 g; 0.1 mol) was heated at 140ºC for twenty minutes. Reaction mixture that is now clear deep brown solution was left at room temperature for four hours. Formed glass like plates of 1,3-dicyclohexylurea (1.3 g) was separated by

filtration. Dimethyl sulfoxide filtrate was diluted with water (1 L). Resulting suspension was stirred at room temperature for thirty minutes and white solid was separated by filtration, washed with water (3x50 ml) and mixed with methanol (150 ml). Resulting methanol suspension was stirred at room temperature for thirty minutes; solid residue was separated by filtration, washed with methanol (3x30 ml) and dried at 110ºC for one hour. In this way pure product in 89% (29.7g) yield was obtained. If necessary product can be purified by crystallization from a large volume of methanol. Mp. 295.1ºC. ^{1}H-NMR (DMSO-d_6, 500 MHz) δ 10.91 (2H, d, *J*=5.5 Hz, NH), 10.46 (2H, s, barbituric acid NH), 3.49 (2H, m, CH), 1.87 (4H, m), 1.66 (4H, m), 1.50 (2H, m), and 1.34 ppm (10H, m). ^{13}C-NMR (DMSO-d_6, 500 MHz) δ 166.8, 160.2 (carbonyl carbons), 149.1, 79.3 (CC double bond carbons) 51.8, 32.6, 24.9, 23.2 ppm (cyclohexane moiety carbons). MS-ES$^+$ (CH_3OH) m/z: 389 (M+CH_3OH+Na^+, 60%), 581 (M+DCU+Na^+, 40%), 805 (M+2DCU+Na^+, 60%), 915 (2M+DMU+Na^+, 35%). Anal. Calcd for $C_{17}H_{26}N_4O_3$ (334.20): C, 61.06; H, 7.84; N, 16.75 Found: C, 61,05; H, 7.89; N, 16.69.

4.10. Preparation of 5-[Di(Cyclohexylamino)Methylene)-1,3-Dimethyl-Pyrimidine-2,4,6-Trione (11).

Compound **11** were prepared by following procedure outlined in *typical procedure B*. Isolated yield is 85%. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 10.97 (2H, d, *J*=7.5 Hz, NH), 3.29 (2H, m), 3.14 (6H, s, CH_3), 1.82 (4H, m), 1.65 (4H, m), 1.46 (2H, m), 1.30 (4H, m), and 1.20 ppm (6H, m). ^{13}C-NMR ($CDCl_3$, 500 MHz) δ 165.3, 160.9 (two carbonyl carbons), 150.8, 81.1 (two CC double bond carbons) 53.2, 33.4, 27.4, 25.2, and 24.2 ppm (four cyclohexane carbons). MS-ES$^+$ (CD_3OD) m/z: 363 (M+1+, 7%), 417 (M+CH_3OH+Na^+, 45%), 609 (M+dicyclohexylurea+Na+, 55%), 747 (2M+Na_+, 75%).

Anal. Calcd for $C_{19}H_{30}N_4O_3$ (362.23): C, 62.96; H, 8.34; N, 15.46 Found: C, 62,89; H, 8.31; N, 15.32.

4.11. Preparation of 5-[di(cyclohexylamino)methylene)-1-phenyl-pyrimidine-2,4,6-trione (12).

Compound **12** were prepared by following procedure outlined in *typical procedure B*. Isolated yield is 95%. ^{1}H-NMR (DMSO-d_6, 500) δ, 10.87 (3H, broad singlet), 7.43 (2H, t, *J*=7.5 Hz), 7.37 (1H, t, *J*=7.5 Hz), 7.21 (2H, d, *J*=7.5 Hz), 3.51 (2H, m), 1.89 (4H, m), 1.67 (4H, m), 1.52 (2H, m), 1.35 ppm (10H, m). ^{13}C-NMR (DMSO-d_6, 500 MHz) δ 165.9, 165.7, 160.1 (three different carbonyl carbons, 149.2, 135.8, 129.4, 128.6, 127.7, 79.8 (aromatic and CC double bond carbons), 52.1, 32.7, 24.9, and 23,4 ppm (cyclohexane moiety carbons). MS-ES$^+$ (CH_3OH) m/z: 433 ($M+Na^+$, 20%), 465 ($M+CH_3OH+Na^+$, 30%), 843 ($2M+Na^+$, 100%). Anal. Calcd for $C_{23}H_{30}N_4O_3$ (410.23): C, 67.29; H, 7.37; N, 13.65 Found: C, 67.12; H, 7.36; N, 13.49.

4.12 Procedure F.

Water solution (30mL) of 1,3-dimethylbarbituric acid (312mg; 2mmol) and 4-dimethylaminopyridine (244mg; 2mmol) was refluxed for 30 minutes. Paraformaldehyde (180mg, 6mmol) was then added into the resulting clear reaction media. Reaction mixture was continuing to reflux for additional 45 minutes. Filtrate was left at room temperature for several hours (overnight). Formed white precipitate was separated by filtration washed with water (3x2ml) and dried under reduced pressure (dessicator) for several hours to afford 520 mg (90%) of pure product.

4-Dimethylamino-1-(1,3-dimethyl-2,4,6-trioxo-hexahydro-pyrimidin-5-ylmethyl)-pyridinium (13) ^{1}H-NMR ($CDCl_3$, 500 MHz) δ δ 8.33 (2H, d, J=8.0 Hz), 6.60 (2H, d, J=7.0Hz), 5.11 (2H, s), 3.25 (6H, s), and 3.16 ppm (6H, s). ^{13}C-NMR ($CDCl_3$, 500 MHz) δ 164.4, 156.2, 153.7, 142.4, 107.1, 83.6, 56.0, 40.2, and 27.5 ppm. MS-ES$^+$ (CH_3COOH, MeOH, and H_2O) m/z: 245.2 (2X4-dimethylaminopyridine+H$^+$), 291.1 (M+H$^+$, 30%), 413.1 (M+4-dimethylaminopyridine+H$^+$), 893.0 (3M+Na$^+$),. Anal. Calcd for $C_{14}H_{18}N_4O_3$ (290.32): C, 57.92; H, 6.25; N, 19.30; O, 16.53.

4-Dimethylamino-1-(2,4,6-trioxo-hexahydro-pyrimidin-5-ylmethyl)-pyridinium (14) ^{1}H-NMR (DMSO-d^6, 500 MHz) 7.63 (2H, d, J=8.0 Hz), 6.35 (2H, d), 4.65 (2H, s), and 2.77 ppm (6H, s). ^{13}C-NMR (DMSO-d^6, 3drop of H_2SO_4, 500 MHz) δ 171.85, 157.72, 139.79, 108.04, 107.75, 75.78, 54.32, 40.54 ppm. MS-ES$^+$ (CH_3COOH, MeOH, and H_2O) m/z: 245.3 (2X4-dimethylaminopyridine+H$^+$), 263.2 (M+H$^+$), 385.2 (M+4-dimethylaminopyridine+H$^+$), 525.4 (2M+H$^+$), Anal. Calcd for $C_{12}H_{14}N_4O_3$ (262.26): C, 54.96; H, 5.38; N, 21.36; O, 18.30.

4.13 Procedure G.

Preparation of 4-Dimethylamino-1-[(1,3-dimethyl-2,4,6-trioxo-hexahydro-pyrimidin-5-yl)-phenyl-methyl]-pyridinium (21). 5-Benzylidene-1,3-dimethyl-pyrimidine-2,4,6-trione, (244 mg; 1mmol) is first dissolved in 200mL of dry acetone (capped 500mL round bottom flask) at 0ºC for 15 minutes. 4-dimethylamino-pyridine (122 mg; 1mmol) is then added and dissolved into the reaction media. The use of senicator bath is recommended to facilitate dissolution. Reaction media is then capped and left in the freezer overnight. Crystals slowly precipitate out. Low boiling point of

acetone allows the concentration of half of the solution by nitrogen flow at 0ºC. Pour 50 mL of anhydrous ether into the flask and leave to stir for 15 minute at 0ºC with capped flask. Filtrate off the remaining crystals (**21**) which dry in the dessicator overnight.

(**21**). ^{1}H-NMR(CD_3OD, 500 MHz) δ 8.26 (2H, d, J=8.0 Hz), 7.30 (2H, t, J=7.0Hz), 7.23 (1H, d), 7.14 (2H, d), 6.89 (1H, s), 6.87 (2H, d), 3.21 (6H, s) and 3.19 ppm(6H, s). ^{13}C-NMR (CD_3OD, 500 MHz) δ 165.4, 158.0, 154.9, 143.5, 139.7, 129.6, 128.7, 108.0, 87.7, 79.0, 70.0, 40.3 and 28.2 ppm. MS-ES^{+} (MeOH) m/z: 245.3 (5-Benzylidene-1,3-dimethyl-pyrimidine-2,4,6-trione+H^{+}), 267.0 (5-Benzylidene-1,3-dimethyl-pyrimidine-2,4,6-trione^{-}+Na^{+}), 367.0 (M+H^{+}), 489.6 (M+5-Benzylidene-1,3-dimethyl-pyrimidine-2,4,6-trione^{+}), Anal. Calcd for $C_{20}H_{22}N_4O_3$ (366.41): C, 65.56; H, 6.05; N, 15.29; O, 13.10.

21'. ^{1}H-NMR(CD_3OD, 500 MHz) δ 8.01 (2H, d, J=8.0 Hz), 7.43 (2H, t, J=7.0Hz), 7.23 (1H, d), 7.14 (2H, d), 6.89 (1H, s), 6.87 (2H, d), 3.21 (6H, s) and 3.19 ppm(6H, s).

1. 4. EXPERIMENTAL reprinted from Tetrahedron lett., Vol. 59; Jursic, B. S.; Douelle, F.; Stevens, E. D. Preparation of 5-Diaminomethylenebarbiturate by Barbituric Acid Addition to Carbodiimide, Pages 3427-3432, Copyright (2003), with permission of Elsevier

REFERENCES

1. Wittig, G.; Felletschin, G. *Ann*. **1944,** *555*, 133

2. Johnson, W. A. *Ylid in chemistry*, *Academic Press New York and London,* **1966**

3. Yanovskaya, L. A. *Russ. Chem. Revs*. **1961**, *30*, 347

4. Doering, W. E.; Hoffman, A. K. *J. Chem. Soc*. **1955**, *77*, 521

5. Wittig, G.; Weigmann, H. D.; Schlosser; M. *Chem. Ber.* **1961**, *94*, 676

5'. Johnson, W. A.; Lacount, R. B. *J. Chem. Soc*. **1961**, *83*, 417

6. Doering, W. E.; Scheiber, K. C. *J. Chem. Soc*. **1955**, *77*, 514

6'. Gutsche, C. D. *Organic reactions, R. Adams, ed, John Wiley and Sons, inc., New York* **1958**, *8*, 364

7. Krohnke, F. *Chem. Ber.* **1935**, *68*, 1177

8. Peichl, E.; Kappe, T. *Arch. Pharm.* **1984**, *317*, 946

9. Geza, S.; Heinrich, W.; Pal, S. *Chem. Zeitung.* **1987**, *111*, 144

10. Fritz, E.; Wrndt, W.; Fenner, H. *Archiv der Pharmazie.* **1978**, *311*, 561

11. Youssif, M. M.; Sarki, S.; Hamana, M. *Heterocycles.* **1981**, *15*, 1083

12. Carter, M. K. *J. Chem. Ed.* **1951**, *28*, 524

13. Gulliya, K. S. *Chem. Abstr.* **1999**, US Patent 5,869,494

14. Sakai, K.; Satoh, Y. *Chem. Abstr.* **2000**, international patent, W099502522A3

15. K. G. *Chem. Abstr.*, **1997** US Patent 5,674,870

16. Gomez, G. G.; Hutchison, R. B.; Kruse, C. A. *Cancer Treatment Rev.* **2001**, *27*, 375

17. Morgan, L. M.; Rogers, A. H.; LeBlanc, B. W.; Boue, S. M.; Yang, Y.; Jursic, B. S.; Cole, R. B. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2193.

18. Morgan, L. R.; Thangaraj, K.; LeBlanc, B.; Rogers, A.; Wolford, L. T.; Hooper, Fan, D.; Jursic, B. S. Manuscript in Preparation.

19. Oliva, A.; De Cillis, G.; Grams, F.; Livi, V.; Zimmermann, G.; Menta, E.; Krell, H. W. *U.S. Pat.* **2002**, US 6,335,332 B1

20. Ashkinazi, R. I. *Int. Pat.* **1999**, WO 99/25699

21. Windholz, M. *The Merck Index* **1983**, *10th edition*

22. Jursic, B. S. *J. Heterocyclic Chem.* **2001**, *38*, 655

23. Morgan, L. R.; Jursic, B. S.; Hooper, C. L.; Neumann, D. M.; Thangaraj, K.; LeBlanc, B. *Biorg. Med. Chem. Lett.* **2002**, *12*, 3407.

24. Wide variety of barbituric acid derivatives are commercially available or can be readily prepared from diethyl malonate condensation with urea 1-substituted, and

1,3-disubstituted urea. For instance see (b) Vogel "A Text-Book of Practical Organic Chemistry, Third Edition, Wiley, New York, N. Y. 1966.

25. For Knoevenagel-type of condensation between aromatic aldehydes and barbituric acid see: (a) De Belin, J.; Romero-Martin, M.-R.; Finn, P. W.; Sayers, L. G.; Law, N. M.; Billington, D. C.; Ryley, S. Bhattacharya, S. *Int. Pat.* **2001**, **WO 01/93841 A2**, (b) Jursic, B. S. *J. Heterocyclic Chem.* **2001**, *38*, 655 and references therein. For double barbituric acid addition to aromatic aldehydes see Jursic, B. S.; Neumann, D. M.; Moore, Z.; Stevens, E. D. *J. Org. Chem.* **2002,** *67*, 2372. For double addition of barbituric acid to isatin see: Jursic B. S.; Stevens E. D. *Tetrahedron. Lett.* **2002,** *43,*5681.

26. For transformation of urea to its more reactive isomer carbodiimide, see: (a) Sandler, S. R.; Karo, W. *Org. Functional Group Prep.* **1971**, *2*, 205. (b) Williams, A.; Ibrahim, I. T. *Chem. Rev.* **1981**, *81*, 589. (c) Appel, R.; Kleinstueck, R.; Ziehn, K. D. *Chem. Ber.* **1971**, *104*, 1335.

27. Gompper, R.; Kuntz, R. *Chem. Ber.* **1985**, *98*, 1391.

28. Wilchek, M.; Miron, T.; Kohn, J. *Anal. Biochem.* **1981**, *114*, 419 and references therein.

29. Some derivatives of 5-diaminobarbiturates **3** were prepared previously through 1,3-dithiolan-2-ylidenebarbiturate, but none of the reported isomers **4**-**12** were prepared with this methods. Figueroa-Villar, J.; Clemente, F. C.; da Silva, A. C. *J. Braz. Chem. Soc.* **2001**, *12*, 247.

30. At this point of our research the only substantial evidence for formation of urea-barbituric acid complex comes from our few ^{1}H-NMR studies. In depth investigation of the complex formation that involves NMR, ES-MS and X-ray study is underway

31. Jursic, B. S. *J. Heterocyclic Chem.* **2001**, *38*, 655

APPENDIX 1

Copyright permission letter

Dear Mr Douelle,

TETRAHEDRON, Vol 59, 2003, Pages 3427-3432, "Preparation of …"

As per your letter dated 4 July 2003, we hereby grant you permission to reprint the aforementioned material at no charge **in your thesis** subject to the following conditions:

1. If any part of the material to be used (for example, figures) has appeared in our publication with credit or acknowledgement to another source, permission must also be sought from that source. If such permission is not obtained then that material may not be included in your publication/copies.

2. Suitable acknowledgment to the source must be made, either as a footnote or in a reference list at the end of your publication, as follows:

   "Reprinted from Publication title, Vol number, Author(s), Title of article, Pages No., Copyright (Year), with permission from Elsevier".

3. Reproduction of this material is confined to the purpose for which permission is hereby given.

4. This permission is granted for non-exclusive world **English** rights only. For other languages please reapply separately for each one required.

5. This includes permission for UMI to supply single copies, on demand, of the complete thesis. Should your thesis be published commercially, please reapply for permission.

Yours sincerely

Helen Wilson

Rights Manager

VITA

Frederic Douelle was born in Chambray-les Tours (France)). In 2000 he first graduated with a D.U.T. from Technological University of Poitiers (France). In 2001, he graduated with a Bsc (first class Hons) from Metropolitan Manchester University (U.K). Enrolled in the Ph.D program at the University of New Orleans since August of 2001, he is currently taking his Master of Science in order to pursue his graduate studies back to Europe. He is a member of the American Chemical Society.