THE STUDY OF ECO – FRIENDLY SYNTHESIS IN BETAINES

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ABSTRACT

The classical synthetic reaction which is considered to be an old and selective but not versatile method for the formation of various derivatives of naphthyridines has been extensively investigated in the past. However, in contrast, few procedures have been developed. Accesses to new methods relying on the microwave irradiated synthesis that easily provide different substituents would be highly desirable. This work was initiated with a desire to discover and predict the green syntheses of some novel meso-ionic compounds i.e. mesomericbetaines.

INTRODUCTION

Modern lifestyle requires directly or indirectly many chemical substances, such as petrochemicals, polymers, pharmaccuticals, agrochemicals, detergents, cleaning and personal care products, paints and coatings, inorganic chemicals, and, more and more urgently, innovative materials; a large part of those consumer products, during the manufacturing, the use and the waste disposal, will be potentially released in the environment, implicating an inevitable (eco)- toxicological hazard for mankind and the environment. Chemistry has provided valuable materials in the form of medicines, food products, cosmetics, dyes, paints, agrochemicals, biomolecules and high-tech substances like polymers, liquid crystals and nanoparticles. Chemists have used their knowledge and skill to prepare a large number of new materials which are far better and more useful than the natural products. Over the past two centuries, fundamental theories in chemistry have been soundly established. Such theories have provided the foundations for the chemical enterprise that generates critical living needs such as food for the world's population, achieves various medical wonders that save millions of lives and improve people's health, and produces materials essential to the present and future needs of mankind. Just less than

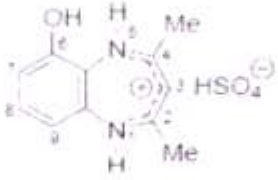
two centuries ago, organic compounds were believed to be only accessible through biological processes under the influence of "vital forces". Today many molecules of great complexity can be synthesized readily. However, despite such enormous achievements, we are facing great challenges in future chemical synthesis. The present state of the art processes for synthesizing chemical products are highly inefficient. The processes on industrial scale involve many chemical reactions using huge quantities and wider varieties of smaller molecules, reagents, solvents, acids, alkali, etc. These chemical processes not only produce the required products but also large quantities ofundesired and harmful substances in the form of solids, liquids and gases and have become the biggest challenge that chemistry has to face So, the pressing need for the synthetic chemists is to minimize chemical pollution. During the last two decades much work has been going on in this direction. The increasing need to reduce pollution and its effects, and the consequent risk for the human health and the environment, has brought towards a new and safer approach to chemical processes and compounds, described as Green Chemistry. The term Green Chemistry was coimed in 1991 by Prof. Paul T. Anastas. The purpose is to design chemicals and chemical processes that will be less harmful to human health and environment. Green chemistry protects the environment, not by cleaning up, but by inventing new chemical processes that do not pollute.

6-Hydroxy-2,4-dimethyl-5H-benzo[b][1,4]diazepin-1-ium hydrogen sulfate (

2,3-Diaminophenol (0.124 g, 1 mmol) was used.

Yield: 0.24 g (92 %).

m.p.: 468–470 K.



(1)

Spectroscopic Data:

^{1}H-NMR (200 MHz, DMSO-d_6): δ = 1.80 (s, 3H, CH_3), 1.89 (s, 3H, CH_3), 4.32 (s, 1H, 3-H),5.99 (d, *J* = 8.2 Hz, 1H, 9-H), 6.54 (d, *J* = 8.2 Hz, 1H, 7-H) , 6.79 (t, *J* = 8.2 Hz, 1H, 8-H),9.12 (s, 1H, NH), 9.62 (s, 1H, NH), 10.75 (s, 1H, OH).

^{13}C-NMR (50 MHz, DMSO-d_6): δ = 24.1 (CH3), 24.2 (CH3), 95.8 (C-3), 113.7, 116.3, 120.3, 129.8, 136.2, 149.9, 175.2, 176.6.

UV λ_{max} (H_2O): 362, 492 nm; λ_{max} (MeOH): 368, 496 nm; λ_{max} (MeCN): 366, 520 nm.

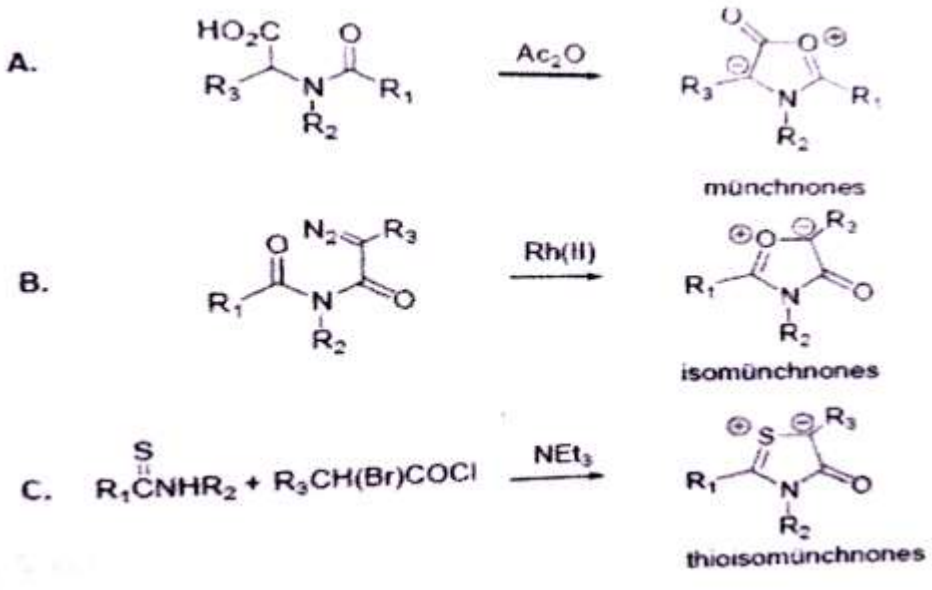
IR (KBr): $\tilde{\nu}$ = 3283, 3050, 1623, 1605, 1519, 1448.

Analytical Data:

Calculated for $C_{11}H_{14}N_2O_5S$ (286.31): C, 46.1; H, 4.9; N, 9.8;
Found: C, 45.7; H, 4.9; N, 9.6.

Mesoinic thiosomunchnones and pyrimidinum betaines

The term mesoionic is generally restricted to five – membered hetrocyclic mesomeric betaines including sydnones, munchnones, and derivaties (iso – and thioisomunchnones). Mesoionic compounds have been known for many years and have been extensively utiliced as substrates for 13 dipolar cycloaddition chemistry The peculiar structure and reactivity of such heterocycles continue to weive considerable attention, espNcially since these mesoionic compounds have heenutitiaed as effective synthones in natural product synthesis. In addition, these compounds have been shown to be good synthons for the synthesis of various fused heterocyclie systems. Perhaps the two most extensively studied mesoionicheteroeyeles are the munchnones and isominchnones. These masked 1,3 - dipoles readily react with a wide variety of double and triple- bond dipolarophites.

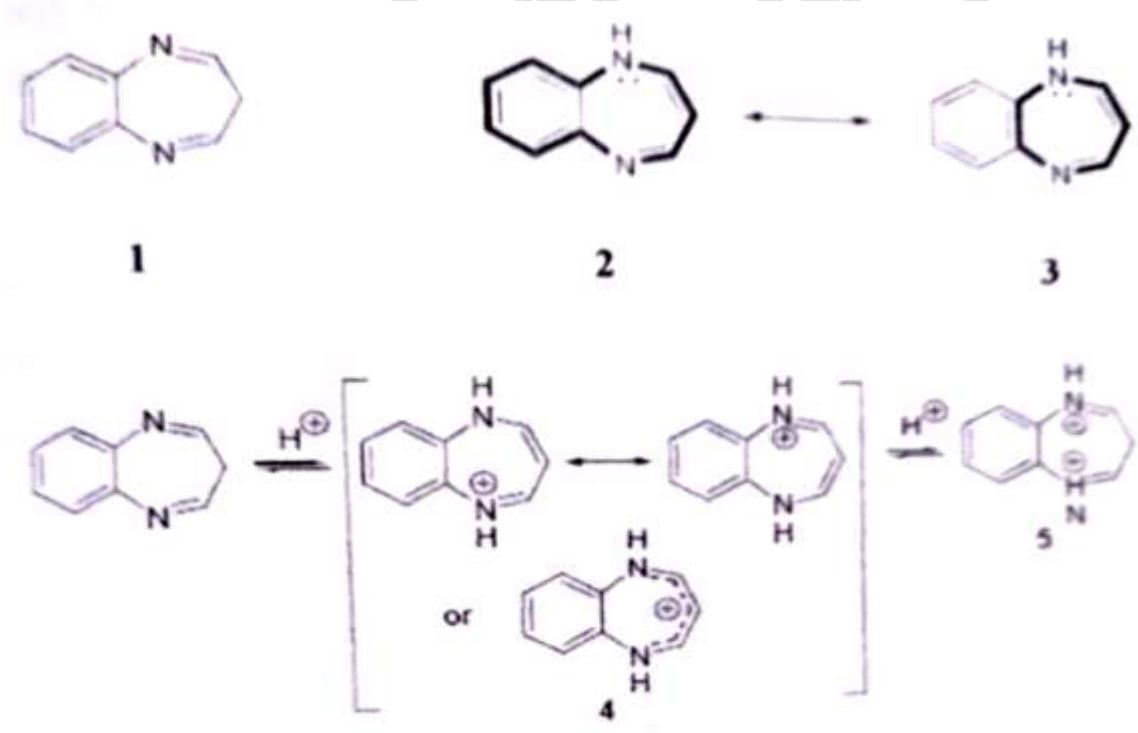


Thioisomunchones which are easily prepared by reaction of N-monosubstitutedthioamidesvith a-haloacyl halides in the presence of NE. contain a thiocarbonylylide dipole within their backbone. Interest in the thioisomunchnone class of mesoions may be attributed to (a) their ease of preparation from simple thioamides, (b) the interesting physical properties they possess, (c) the propensity for its thiocarbonylylide dipole to undergo 1,3-dipolar cycloaddition with a wide range of dipolarophiles to produce complex heterocyclic ring systems. Potts and co-workers have extensively studied the biomolecular cycloaddition behaviour of thioisomünchnone. On the other hand, during the

last decades the synthesis of six-membered heterocyclic pyrimidiniumbetaines has been extensively studied which are regarded as being good cycloadducts for 1,4- type cycloaddition reactions with electron-poor or electron-rich multiple bond systems. In recent years, much attention has been focused on the biological and pharmacological activities of bicyclic six-membered betaines, which are still unexplored. These betainic heterocycles have wide industrial applications e.g. as a non-aqueous electrolyte battery and pressure transfer photothermographic copying materials; some show even marked hair-growth stimulation.

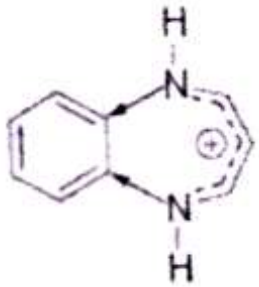
1,5-Benzodiazepines

Benzodiazepines usually occur in the diimine form 1 rather than in the conjugated vinamidine forms depicted in formulas 2 and 3. In the diimine form 1, some extra stabilization arises from the conjugation of the imine groups with the benzene ring. Cyclic conjugation as in 2 and 3 may indeed lead to destabilization of the molecules because it involves interaction of 12 n-electrons around the periphery of the molecule as implied in 2 or of 8 n-electrons around the 7- membered ring as in 3; cither of these are destabilizing 4n n-electron systems. Protonation of benzodiazepines leads to the successive formation of monocations 4 and dicationes 5.



The conjugated form, which would have eight n-electrons associated with the 7-membered ring, is electronically an analog of benzocyclooctatetraene. Annular conjugation around either the diazepine ring or the overall periphery makes no positive contribution to the stability of the system, whereas electronic interaction between the benzene ring and the two imino groups in the imino form does.

With a few exceptions the bases are colorless or pale yellow, as are the dications, which must exist as bisiminium salts. In contrast, the monocations are intensely colored, commonly purple or blue. Formation of the monocation involves setting up a stable 6 n-clectronvinamidinium system; such systems have stabilization energies of the order of 20 Kcal/mol. There is energetic advantage in generating the stabilized vinamidinium system, but there is disadvantage if it interacts appreciably with the 6 n-electron system of the benzene ring. To minimize such interactions, the bonds linking the nitrogen atoms to the benzene ring are long for aryl C-N bonds. More recently a number of X-ray structure determinations have been carried out. As evidenced by calculations and X-ray single crystal structural analyses, the positive segment of the molecule are separated from the benzene ring by long C-N bonds to decrease the possibility of 4n circuit of n-electrons. Thus the benzene ring and the vinamidiniummoicty in known molecules are more or less isolated systems as exemplified by 6.

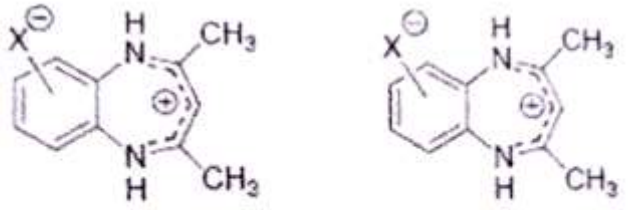


1,5-Benzodiazepines have been rather overshadowed by the isomeric 1,4-benzodiazepines, which have been of enormous pharmacological interest, largely because of their very wide use as tranquillizers. Some 1,5-benzodiazepines also have physiological effects, inter alia, some 2-amino-4-phenyl derivatives as tranquillizers and some 2-p-fluorophenyl-4-phenyl-8-chloro derivatives as antidepressant agents (in mice). Some 2-amino-methylthio derivatives act as depressants of the central nervous system and anticonvulsants, whereas 2,4- diaminoanalogs act as stimulants of the central nervous

system convulsants. Certain benzodiazepines, in particular 2-thioderivatives, show antibacterial activity, whereas some 2,4-dimethyl derivatives are said to inhibit the growth of certain sarcomas in rats. Post emergence herbicidal activity has been shiown by certain benzodiazepines.

Anti – huckel mesomeric betaines

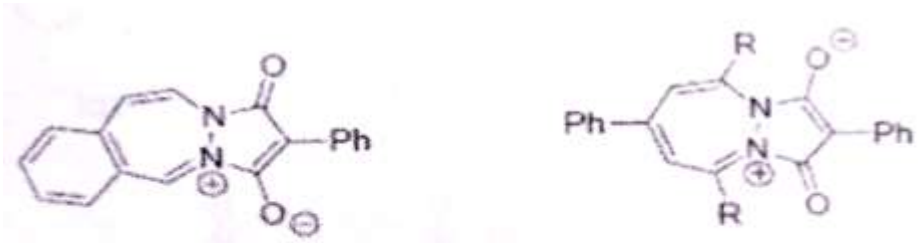
Whereas the first comprehensive classification of mesomeric betaines by Ollis,. Stanforth, and Ramsden in 1985 resulted in a better understanding of 5- and 6-membered ring lieteroeyclic compounds, however, it is apparent that until now niv a little information is available on 7- membered heterocyclic mesomericbetaimes Most of them rapidly decomposed after formation, or attempts made to syntheaze them were failed. Obviously, the reason for these instabilities is the pmber of (4n) π-electrons in the cationic part, which contradicts the Hückel rule of anomaticity. We became interested in 1,5-benzodiazepine derivatives, which wonldreaul tfom an intramolecular proton shift and the formation of betainicdructures An additional impetus was the interesting game with the number of x-decarons delocalised in such systems. We intended to investigate here the gytieses and properties of 2,4-dimethylmonosubstituted-6,7-benzo-1,5- dieneinium salts as hydrogen sulfate, trifluoroacetate, and picrate which on deprotionation of the susceptible acidic group on benzene ring would lead to the comenponding stable 7-membered ring mesomericbetaines.



ANTLHICKEL 7-MEMBERED RING MESOMERIC BETAINES

Since the first preparation of a mesomericbetaine (MB) by Emil Fischer and the rosognition that certain representatives play important biological roles as avodified nucleobases or alkaloids, this class of compounds were found of considerable interest as valuable starting materials for the synthesis of heterocycles ond natural product analogs,

drugs, or indicators. However, the existence of 7- membered ring mesomericbetaines was rarely reported. The structures 7 and 8 are mentioned in the literature. The betaine 7, which was only identified by mass spectrometry, rapidly decomposed in solution. The syntheses of 8a and 8b failed (Scheme-4.4). These observations are due to the number of 4n n-electrons (n = 3 or 2) in the cationic part, which contrasts with the Hückel rule.



7 **8**

8a: R = Ph & 8b: R = 4-C_6H_4OMe

For the case of the benzo[b][1,4]diazepinium (1,5-benzodiazepinium) ring system, we intended to take advantage of the destabilizing number of electrons to force a charge separation to a mesomericbetaine as shown in Scheme-4.6. It is known that the diimine form XIII of this ring system, from which numerous examples have been described, is more stable than the conjugated form XII. The latter would have 4n n-electrons associated with the 7- membered ring, which is electronically an analog of benzocyclooctatetraene. There is no positive contribution to the stability of the system by annular conjugation around either the diazepine ring or the overall periphery.

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