In the Name of Allah

the Beneficial the Meraiful

Razi University

Faculty of Chemistry
Department of Organic chemistry

M.Sc.Thesis

Title of the Thesis:

Single-step synthesis of multi-compunent spirobarbiturates using ionic liquids & Synthesis of substituted pyridine filled with catalysts supported on solid substrate

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By:

Forough Monjezi

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Abstract:

In this thesis, a better reaction conditions for the synthesis of spirobarbiturates catalyzed by task-specific ionic liquid (2-hydroxy-N-(2-hydroxyethyl)-N,N-dimethylethanaminium formate), calcium hypochlorite $Ca(OCl)_2$ or N-Bromosuccinimide (NBS) in the presence of water at room temperature by ultrasonic technique is provided. The design and synthesis of spirocycles is a challenging task because it involves the creation of a quaternary center, which itself is considered to be one of the most difficult tasks among synthetic transformations.

The spirobarbiturates through one-step multicomponent reaction (MCR) of aldehydes, N.N′-dimethylbarbituric acid and catalyst by ultrasonic technique with high efficiency and no side products are produced. This method has advantages compared with previous methods such as simple reaction conditions, short time, the reaction environment safety and ease the separation of synthesis products after the reaction.

In the second part of this project a one-pot, three-component condensation of malononitrile and thiols with aromatic aldehydes, containing either electron-donating or electron-withdrawing groups, catalyzed by biguanide-supported SBA-15(SBA-15-Met) in ethanol at temperature 50 ?C conditions to produce highly substituted pyridines in high conversion is reported.

Also in the third part of this project, an efficient process multi-component reaction of various thiols and malononitrile with aromatic aldehydes, containing either electron-donating or electron-withdrawing groups, catalyzed by ion exchange resin (ion exchange III) in acetonitrile at room temperature conditions to produce highly substituted pyridines in high conversion is reported.

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Forough Monjezi

Dedicated to:

My Dear Family

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Chapter one

Introduction

1.1. Introduction to the organic materials and their medicinal properties

The very foundations of biochemist try, biotechnology, and medicine are built on organic compounds and their role in life processes. Almost all of the modern, high-tech materials are composed, at least in part, of organic compounds. Clearly, organic chemistry is critically important to our high standard of living. Pharmaceuticals are also comprised mainly of organic compounds. The role played by organic chemistry in the pharmaceutical industry continues to be one of the main drivers in the drug discovery process. The foundation of the pharmaceutical industry is its large pool of highly skilled organic chemists. Indeed, organic chemists have produced a wonderful myriad of highly successful products to fight human diseases. Nearly all modern pharmaceutical agents are first designed, synthesized, and optimized by organic chemists working in collaboration with biologists.[1, 2]

The discipline of medicinal chemistry is devoted to the discovery and development of new agents for treating diseases. Most of this activity is directed to new natural or synthetic organic compounds. Inorganic compounds continue to be important in therapy, e.g., trace elements in nutritional therapy, antacids and radiopharmaceutical activities are clearly dominant. Development of organic compounds has grown beyond traditional synthetic methods. It now includes the exciting new field of biotechnology using the cell's biochemistry and organic chemistry to synthesize new compounds.

Most chemists work with a team of scientists from different disciplines, including biologists, toxicologists, pharmacologists, theoretical chemists, microbiologists, and biopharmacists. Together this team uses sophisticated analytical techniques to synthesize and test new drug products and to develop the most cost-effective and eco-friendly means of production.[3]

1.2. Barbiturates and spirobarbiturates

Barbituric acid was discovered in 1864 by Adolf von Baeyer as the first of a group of sedatives known as barbiturates. He prepared barbituric acid from a fusion of the urea and malonic acid[4] (Figure 1.1). Barbituric acid has been used in the manufacturing of plastics[5a] textiles[5b] polymers[5c] and pharmaceuticals.

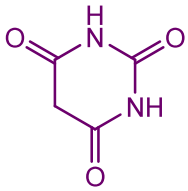


Figure 1.1

Barbiturates as drug produce a wide spectrum of central nervous system responses. The nature of response depends on their half life which can be quite short (several minutes), longer (one to two days) or very long (four to five days). The duration of the drug's effect depends on their solubility in lipids or water. Solubility is dependent on the substituent groups present on the barbituric acid. Derivatives of barbituric acid constitute one of the more venerable families of medicinal agents; the first member of the series, barbital, has been in continuous use since 1903.[6]

Barbiturates possess a rather wide range of therapeutic activities.[7] In particular, drugs belonging to this class of compounds have been used for more than a century as hypnotics and anticonvulsants. Pharmaceutical industries market more than 50 barbiturate derivatives under various trade names.[8]

Pharmacologically active barbituric acid derivatives are either mono or di-C-alkylated derivatives. There are some molecular systems that are capable of modulating human immune responses, thus effectively opening an avenue for new and innovative treatments that combat terrible diseases such as AIDS[9] and cancer. Generally, these compounds have been used as sedative hypnotics or local anesthetics. In addition to the pharmaceutical value, they are also useful building blocks in assembling supramolecular structures via noncovalent interactions.[10] In this respect, Fenniri et al. devised helical nanotubes in 2001.[11] It is well established that barbituric acid and 2-thiobarbituric acid undergo Knoevenagel condensations with aldehydes to give 5-substituted derivatives.[12] 5-Substitued barbiturates have been predominantly used for their anticonvulsant[13] and

sedative-hypnotic[14,15] properties. 5-Monoalkylated barbituric acids like 5-(benzyloxy)benzyl barbituric acids are used in the treatment of cancer and AIDS via inhibition of human uridine phosphorylase (Urd Pase).[16] 5-Arylidine-1,3-dimethylbarbiturates behave as phototypes of NAD and FAT and cause oxidation of alcohols and thiols to carbonyl compounds and disulfides respectively.[17] Morever, 5-monosubstituted barbiturc acids are the versatile synthones for procuring the C-5 substituted antiviral drugs. 5,5-Disubstituted barbituric acids do play a significant role as sedative and stimulant agents.[18]

Until 1999 barbituric acid derivatives were mostly used as sedative and anesthetic drugs,[19] however, more nontraditional uses for barbiturates may become predominant in medicinal chemistry due to the fact that recent results suggest that some aromatic-dibarbiturates may possess anticancer activity by modulating human immune responses.[20] A major problem associated with these compounds is the evaluation of the biological properties of aromatic-dibarbiturates, namely because there are not many derivatives available for testing, and those that are available do not have sufficient solubility in aqueous media. Unfortunately, procedures for the preparation of aromatic and heterocyclic dibarbiturates are not available.

Barbiturate groups are strongly electron-withdrawing because they gain aromatic stabilisation upon reduction.[21] This property has been exploited in the preparation of molecules which possess very pronounced quadratic non-linear optical (NLO) properties, of interest for potential applications in opto-electronic and photonic technologies.[22]

Amongst different heterocyclic systems, the chemistry of barbituric acid and their derivatives has drawn much attention due to their broad spectrum of chemotherapeutic properties such as hypnotic, antitumor, antiviral, anticonvulsant, analgesic and toxic.[23,24] Also, this class of barbituric acid based on spiro compounds, exhibit anticonvulsant,[25] narcotic and analgestic properties[26] and act as dihydroorotate dehydogenase inhibitors.[27]

Spiro barbital (Figure 1.2) is a barbiturate derivative invented in 1970s.[28] It has hypnotic and sedative effects, and has a moderate potential for abuse.

Figure 1.2 The typical structure of spiro barbital

Organic molecules in which one carbon atom is common to two rings are called spirocyclic compounds. In other words, spiro compounds are structures having one atom (usually a quaternary carbon) as the only common member of two rings (Figure 1.3).

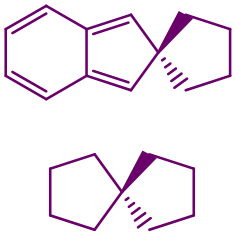
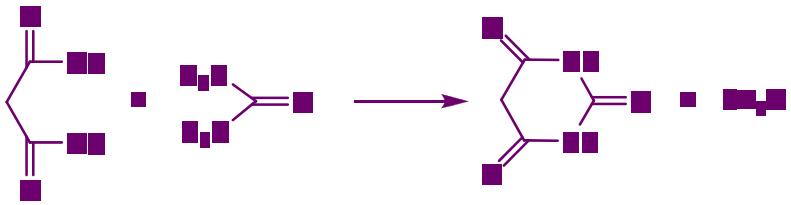


Figure 1.3. The typical structure of spiro barbital spiro compounds

1.3. Synthesis of barbiturates and spiro barbiturates

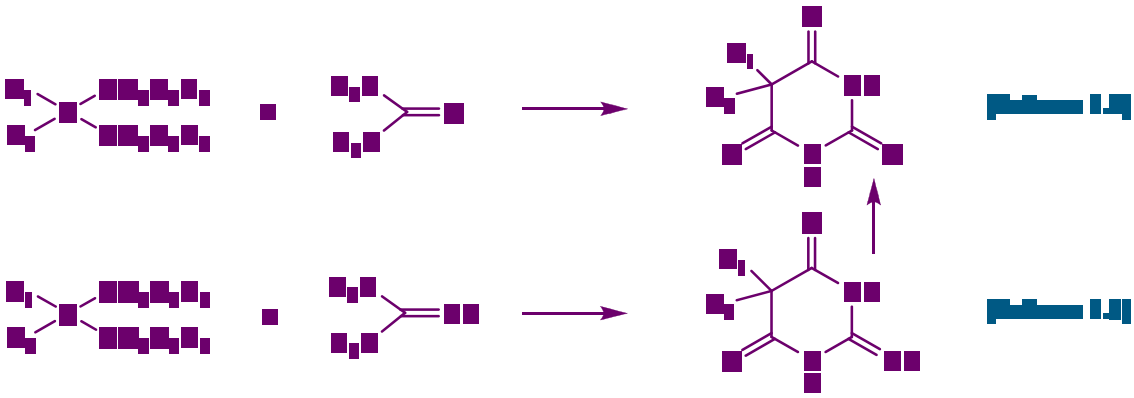
1.3.1. Synthesis of barbiturates

The first compound of barbiturates derivatives, barbituric acid, prepared from a fusion of urea and malonic acid[4] (Scheme 1.1).



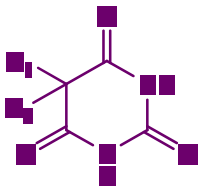
Scheme 1.1. Production of barbituric acid

The final step in the synthesis of all barbiturates consists in either condensation of a suitably substituted malonic or cyanoacetic ester with urea by means of sodium ethoxide (scheme 1.2) or analogous condensation of such an ester with guanidine followed by hydrolysis of the imine thus produced[29](Scheme 1.3).



Some barbituric acid derivatives are presented in table 1.

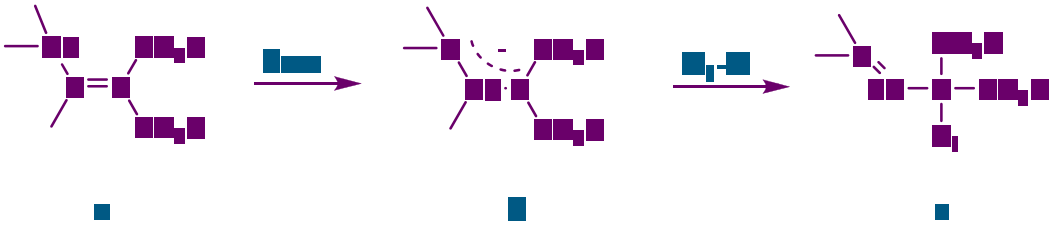
Table 1. Derivatives of barbituric acid



Generic name	R_1	R_2
Barbital	CH_2CH_3	CH_2CH_3
Butethal	CH_2CH_3	$-(CH_2)_3CH_3$
Hexethal	CH_2CH_3	$-(CH_2)_5CH_3$
Probarbital	CH_2CH_3	CH_3-CH-CH_3
Butabarbital	CH_2CH_3	CH_3-CH-CH_2CH_3
Pentobarbital	CH_2CH_3	CH_3-CH-$CH_2CH_2CH_3$
Phenobarbital	CH_2CH_3	C_6H_5

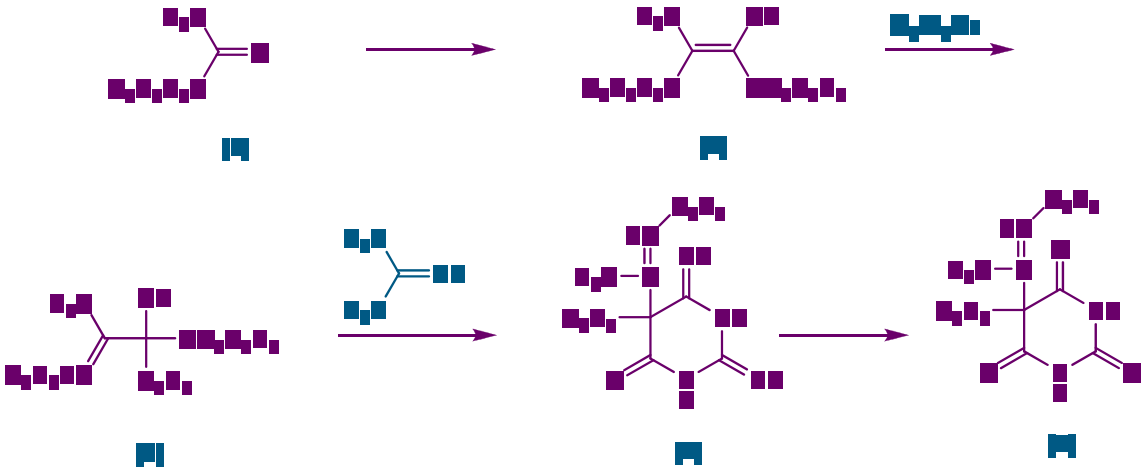
1.3.1.1. Synthesis of monosubstituted barbiturates

Treatment of an ethylidene malonic ester such as **(a)** with strong bases results in loss of a proton from the allylic position to produce the ambident ion **(b)**. Alkylation of such carbanions usually occurs at the carbon bearing the carbonyl groups, resulting in the establishment of a quaternary center and deconjugation of the double bond **(c)** (Scheme 1.4).



Scheme 1.4

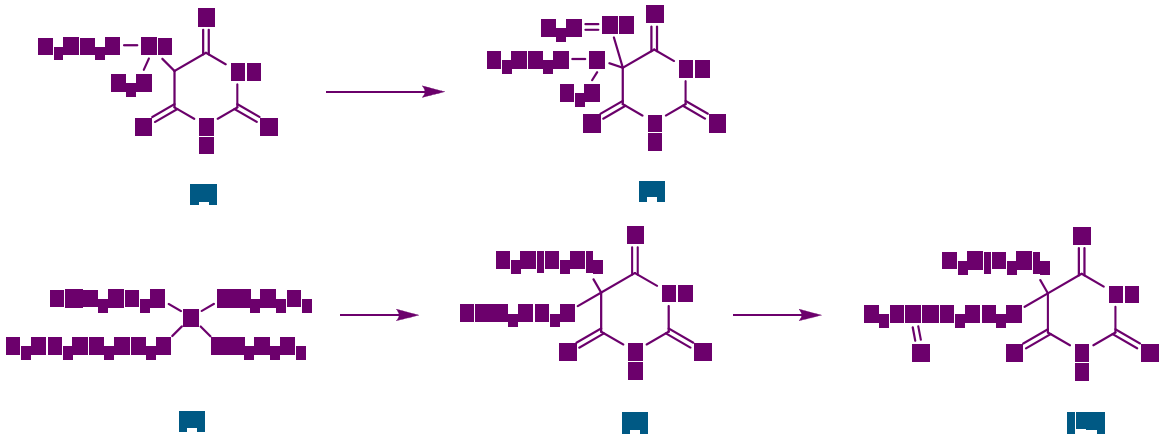
An early application of this reaction to the preparation of barbiturates starts by the condensation of the ketone, **(1)**, with ethyl cyanoacetate via Knoevenagel reaction. Alkylation of the product **(2)** with ethyl bromide by means of sodium ethoxide affords **(3)**. Condensation of this intermediate with guanidine in the presence of sodium ethoxide gives the diimino analog of a barbiturate **(4)**. Hydrolysis affords vinbarbital **(5).**[30, 31] (Scheme 1.5) Application of this scheme to condensation products of cycloalkanones affords the cycloalkenyl-substituted barbiturates.



Scheme 1.5

1.3.1.2. Synthesis of disubstituted barbiturates

Reaction of the monosubstituted barbiturate, **(6)**, with ethylene at elevated temperature and pressure in the presence of a zinc catalyst affords butylvinal **(7)**.[32] Alkylation of the anion from diethyl butylmalonate with ethylene oxide affords the malonate containing a hydroxyethyl side chain **(8)**. This is then converted to the barbiturate **(9)** in the usual way. Treatment of the product **(9)** first with phosgene and then ammonia affords the carbamate carbubarbital **(10)** [33] (Scheme 1.6).

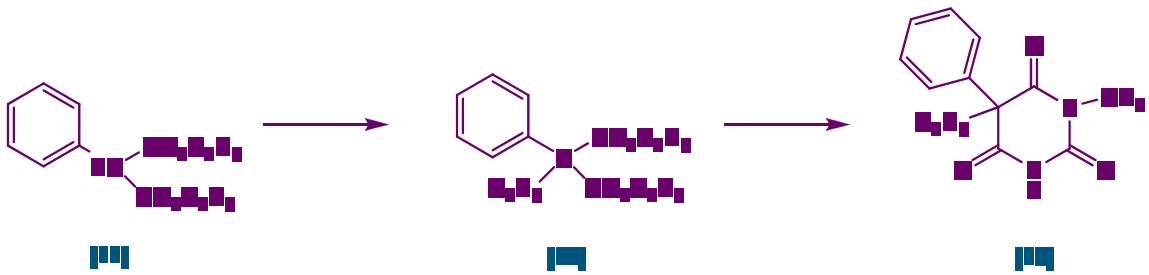


Scheme 1.6

Also, 5,5-disubstituted barbituric acids are prepared by the condensation of substituted diethyl-malonic esters and urea in the presence of a base[18] and by palladium catalyzed asymmetric allylic alkylation of barbituric acids.[34]

1.3.1.3. Synthesis of barbituric acids bearing a methyl group on nitrogen

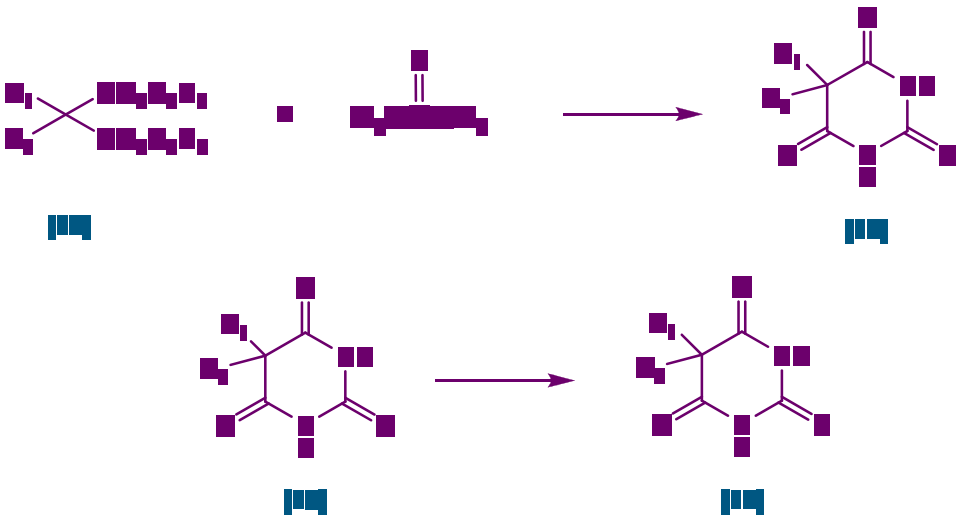
Condensation of disubstituted malonic ester with N-methyl urea yields the corresponding barbituric acids bearing a methyl group on nitrogen. (The plane of symmetry that bisects these molecules, of course, makes both nitrogens identical.) Carbethoxylation of ethylphenylacetate (sodium hydride and ethylchloroformate) affords diethylphenylmalonate **(11)**. Alkylation with ethylbromide gives **(12)**. Condensation of **(12)** with N-methyl urea in the presence of base gives mephobarbital **(13)** [35] (Scheme 1.7).



Scheme 1.7

1.3.1.4. Synthesis of thiobarbiturates

Replacement of the oxygen on the carbonyl group at the 2 position by sulfur affords a series of sedative-hypnotic agents that tend to show both faster onset and shorter duration of action than their oxygenated counterparts. These compounds are obtained in a manner quite analogous to the oxygenated analogs, that is, by condensation of the appropriate malonic ester with thiourea in the presence of a strong base. Thus, reaction of **(14)** with thiourea gives thiopental **(15)**.[36] It is of note that although the drug can be prepared by the above route, reaction of barbital **(16)** with phosphorus pentasulfide constitutes an alternate route to thiobarbital **(17)** [37] (Scheme 1.8).



Scheme 1.8

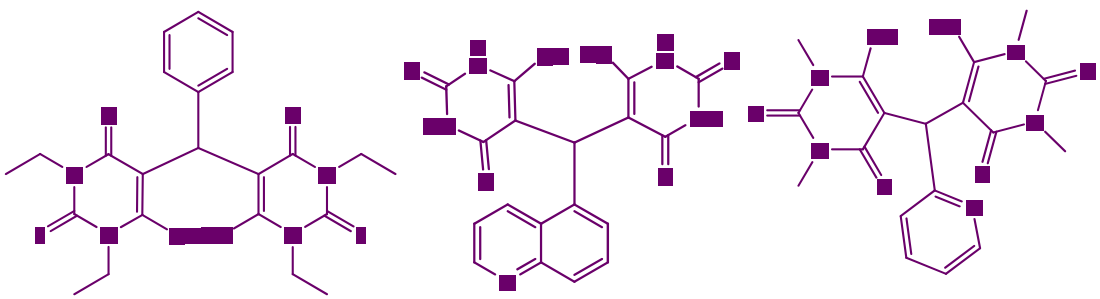
1.3.1.5. Synthesis of barbituric acid benzylidenes

Knoevenagel condensation is one of the elemental reactions in organic chemistry. Traditionally, it is carried out in the presence of a base catalyst[38a] *e.g.*, ammonia, amine and their salts. For its importance in organic synthesis, many catalysts such as aluminum oxide,[38b] xonotlite,[38c] $AlPO_4Al_2O_3$,[38d] KF-Al_2O_3,[38e] K_{10}-$ZnCl_2$,[38f] cadmiumiodide[38g] and KF montmorillonite[38h] have been reported as useful catalysts for Knoevenagel condensation. Generally this reaction is performed in organic solvent, such as benzene, ethanol or DMF. Some examples of barbituric acids benzylidenes are represented in Scheme 1.9.

Scheme 1. 9

1.3.1.6. Synthesis of bis barbituric acids

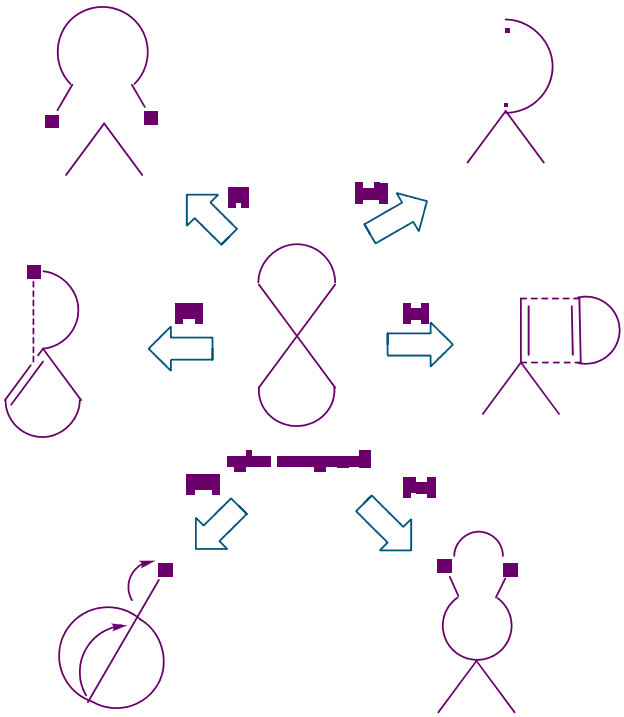
A series of bis barbituric acid has been synthesized by Jursic in the trifluoroacetic acid and methanol as solvent.[39] NMR reaction following experiments have been used by Jursic and Neumann to find optimal conditions for the barbituric acid double addition to aromatic and heteroaromatic carboxaldehydes. It is established that aromatic aldehydes with electron-donating substituents such as hydroxy, methoxy, and dimethylamino produce only the single addition barbituric acid adduct (barbituric acid benzylidenes). If these electron-donating substituents are transformed into electron-withdrawing substituents by virtue of protonation (NMe_2 to $^{+}NHMe_2$) then the double barbituric acid adduct becomes the sole product of the reaction. This is also true regardless of the reaction media if strong electron-withdrawing substituents (such as a nitro group) are present. Considering that the reactive species for nitrogen containing aromatic heterocycles are actually the conjugated acids (electron deficient molecule) only the double barbituric acid can be isolated.[40] some examples of bis barbituric acids are reperesented in Scheme 1.10.



Scheme 1.10

1.3.2. Synthesis of spiro barbituric acids

The design and synthesis of spirocycles is a challenging task because it involves the creation of a quaternary center, which itself is considered to be one of the most difficult tasks among synthetic transformations. Some recent approaches based on metathesis, cycloaddition and transition-metal-mediated transformations to spirocycles are shown in Figure 1.4.



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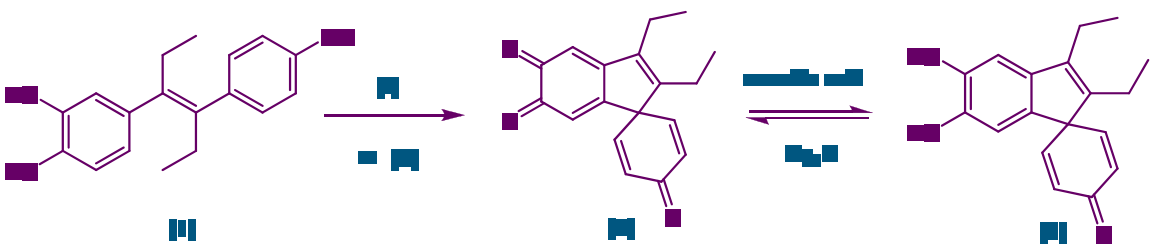
One reported example of these approachs is reperesented below which is called oxidative cyclization method (OCM):



Scheme 1.11: (i) Ag_2O (6 equiv), CH_2Cl_2, r.t, 10 min, 99% or (ii) Ag_2O (6 equiv), CH_2Cl_2, 0 $^{\circ}$C, 30 min,40%

When the stilbene derivative (**1**) is treated with six equivalents of silver oxide in dichloromethane at room temperature, electroactive moiety of **1** is oxidized to quinone followed by an intramolecular cyclization process. Excess oxidizing agent present in the reaction mixture further oxidizes catechol (**3**) into spiroquinone (**2**). [41]

The following chiral spiro nucleoside containing the barbituric acid moiety was efficiently synthesized from optically pure precursors by Mitsuharu Kotera et al in 2001. They established that this spiro barbituric acid nucleoside can be used as building blocks in modified oligonucleotide synthesis in view of applications such as antisense and antigene strategies[42](Figure 1.5).

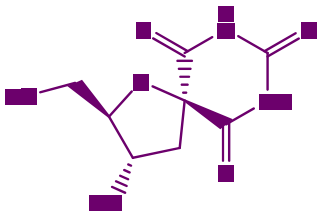


Figure 1.5

An interesting class of spiro-barbiturates that are potent inhibitors of MMP-13 has been synthesized by Soong-Hoon Kim in 2005[43]. The matrix metalloproteinases (MMPs) belong to a family of zinc proteases that are important inhomeostasis of extra-cellular matrix proteins.[44] They have been implicated in several pathologies including cancer, osteoarthritis, and rheumatoid arthritis[45] (Figure 1.6).

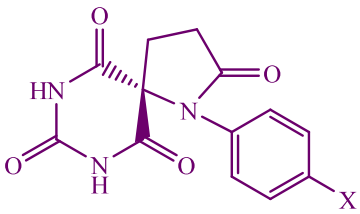


Figure 1.6

A series of spirobarbiturates has been synthesized by Shailee Kesharwani in 2009 using an appropriate synthetic route. All the synthesized compounds were screened in vivo for their anticonvulsant activity and acute toxicity. These compounds were administered at doses of 30, 100, 200, and 300 mg/kg body weight and the anticonvulsant activity was noted at 1 h time intervals after drug administration. All the synthesized compounds were evaluated for the phenobarbitone-induced hypnosis potentiation test and showed sedative-hypnotic an anticonvulsant activity[46] (Figure 1.7).