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"On-water" catalyst-free, one-pot synthesis of quaternary centered and spiro-tetrahydrothiophene-barbiturate hybrids

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ABSTRACT

A green and efficient method have been developed for the synthesis of quaternary centered and spiro-barbiturate-tetrahydrothiophene hybrids *via* Knoevenagel condensation,1,4-thia-Michael and intramolecular Aldol reactions using "on water" concept under catalyst-free conditions. Systematic studies were carried out to find the role of the water and total reaction concentration (0.086 M) to promote the reaction in two steps (one-pot). The use of water as a reaction medium, catalyst-free conditions, broad substrate scope, one-pot approach for the creation of quaternary centered and spiro molecules are the advantages of this method.

Tetrahydrothiophenes (thiolanes) are found in many biologically active molecules and natural products of Salacia family,[1a,b] tetronothiodin,[1c] breynolide,[1d] and biotin,[1e] The tetrahydrothiophene containing natural products and semi-synthetic compounds play role in the fatty acids synthesis (biotin) and work as potent inhibitors of α-glucosidase,[1a] HIV, hepatitis-B,[2] and antagonist for cholecystokinin type-B (tetronothiodin),[1c] agonists of selective A3 adenosine receptors,[3] Also, the thiolane can be used as a precursor for functionalized thiophenes, which are useful in medicinal and materials chemistry.[4] The synthesis of the functionalized (β-hydroxy)/fully substituted tetrahydrothiophenes (present in many biologically active compounds; Fig. 1) is challenging and involve tedious protocols by conventional methods.[1a,b] This has been addressed recently by using 1,4-dithiane-2,5-diol with electron deficient olefins under basic conditions.[5]

The α,α-dicyanoolefines are excellent synthons in organic chemistry and used for the synthesis of complex and advanced intermediates with quaternary centers, natural products, and medicinally important molecules. Along with these, the α,α-dicyanoolefines are used as acceptor, donors (nucleophiles) and dienophiles in Michael, vinylogous and cycloaddition reactions respectively.[6]

The barbituric acid derivatives (including spirocycles) are well-known in medicinal chemistry.[7] Some of the recent reports indicate that these molecule can be used as inhibitors of α-glucosidase,[8] anticonvulsant,[9] antitumor,[10] antiepileptic,[11] anesthetic and sedative,[12] anti-cancer,[13] anti-AIDS,[14] hypnotic,[15] TNF alpha converting enzyme inhibitors,[16] and MMP-13,[17] agents (Fig. 2). One of the best methods to synthesize spiro-barbituric acid derivatives is using barbiturate olefins which can be easily obtained by the condensation reaction between barbituric acid and corresponding carbonyl derivatives (aldehydes and ketones). These intermediates can also be used as acceptor, donors (nucleophiles) and dienophiles in Michael, cycloaddition reactions similar to α, α-dicyanoolefines and can be used for the synthesis of three, five and six member rings.[18]

Most of the biochemical processes in living organisms are based on the water because of its unique properties. Whereas, in synthetic organic chemistry, water was a least preferred solvent because of its reactivity with some of the functional groups and the solubility problem of organic molecules. But after pioneering findings of "on water" concept by Sharpless and Breslow groups,[19] the use of water is increasing in organic synthesis by using "in water" and "on water" concepts. Also, the mechanistic and kinetics studies supporting the role of water in acceleration of the reaction, bringing the reactants together and stabilization of activated transition state by hydrogen bond formation is well documented in the literature.[20] The natural abundance makes water as a cheap and green solvent for the organic transformations. Also, in most of

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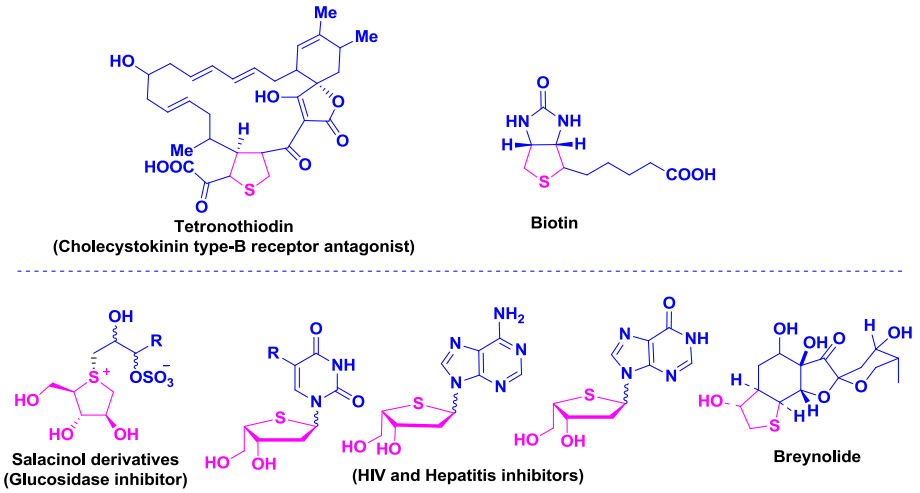

Fig. 1. Biological active compounds with thiolane moiety.

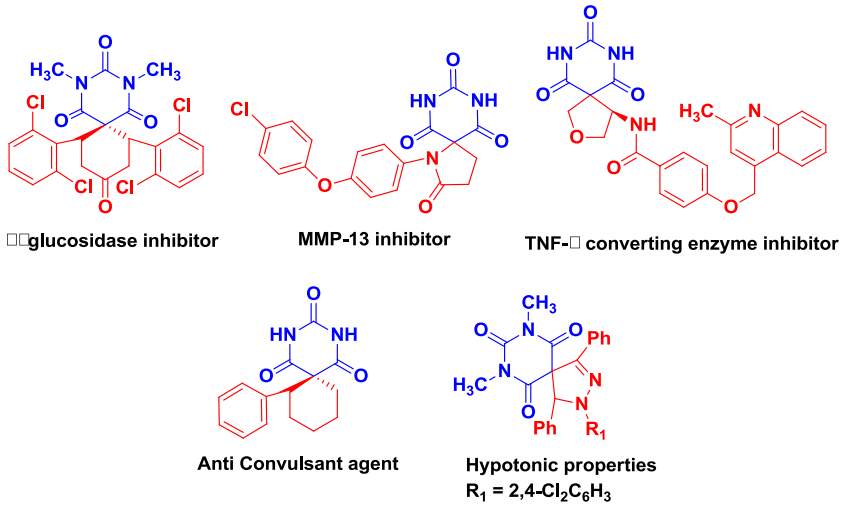

Fig. 2. Biological active compounds with barbituric acid moiety.

the water-mediated organic reactions, the product formed is a solid which is easily isolated from the reaction by simple filtration or washing with common organic solvents (when required). Because of these, there is a drastic increase in the water-mediated reactions in past couple of years. Still, there is a demand to develop the green and environmentally friendly approaches for medicinal chemistry programs and industry applications.

Consecutive/one-pot reactions are the chemical processes in which two or more consecutive reactions and multiple bonds formation occurs in a sequential manner where the process of each step depends on the compounds/intermediates that are formed in the earlier step. These reactions are one of the best methods in synthetic organic chemistry to prepare complex and diversified molecules with a simple set of starting materials, avoiding the isolation and purification of the intermediates and reducing the chemical waste. Because of these advantages, consecutive/one-pot reactions got much attention and extensively used in the methodology development, total synthesis, process research, heterocyclic, medicinal (library generation) and industrial chemistry using green chemistry aspects such as atom economy and sustainability.[20,21]

The generation of a new quaternary center with all carbons substitution is a difficult task under conventional methods, which may be due to the reactivity of the starting materials, steric effects and also non-availability of suitable reactive partners to generate quaternary center.[22] Many of these methods involve the use of catalysts and organic solvents.[23] However, the use of aqueous medium under catalyst-free conditions has not been explored for these type of reactions where all-carbon quaternary centers are generated.[24] Also to the best of our knowledge, there is no report for the synthesis of tetrahydrothiophenes using barbiturate olefins and α,α-di-cyanoolefins with 1,4-dithiane-2,5-diol and also for the "on-water" concept under catalyst-free conditions for the synthesis of spiro and quaternary centered tetrahydrothiophenes using 1,4-dithiane-2,5-diol.

Keeping in view of above all, considering the medicinal importance of the spiro-barbiturates, tetrahydrothiophenes and quaternary centered molecules, and in continuation of our interest in environmental friendly green synthetic methods,[5c,25] we herein report a simple, straight forward and catalyst-free method using one-pot reactions of aldehydes with barbituric acid/malononitrile and 1,4-dithiane-2,5-diol to give a new family of quaternary centered and spiro-barbituric acid-tetrahydrothiophene hybrids and functionalized tetrahydrothiophene derivatives in one-pot sequence under green conditions using "on water" concept.