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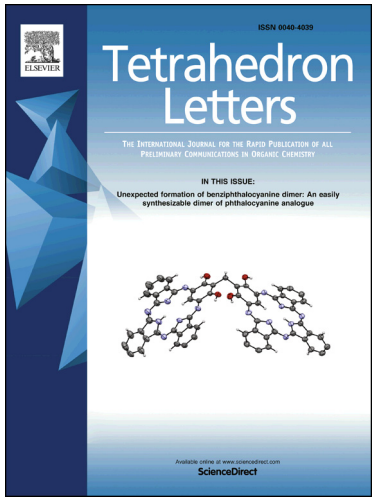

"On-water" catalyst-free, one-pot synthesis of quaternary centered and spiro-tetrahydrothiophene-barbiturate hybrids [§]

Sakkani Nagaraju, Kota Sathish, Banoth Paplal, Dhurke Kashinath

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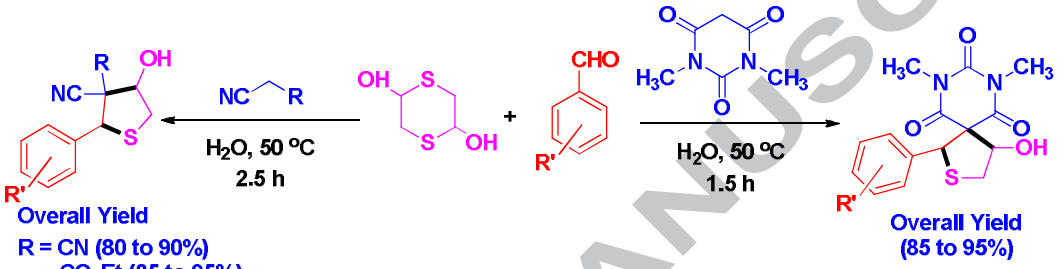
Sakkani Nagaraju, Kota Sathish, Banoth Paplal and Dhurke Kashinath*



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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; **Figure-1**[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]

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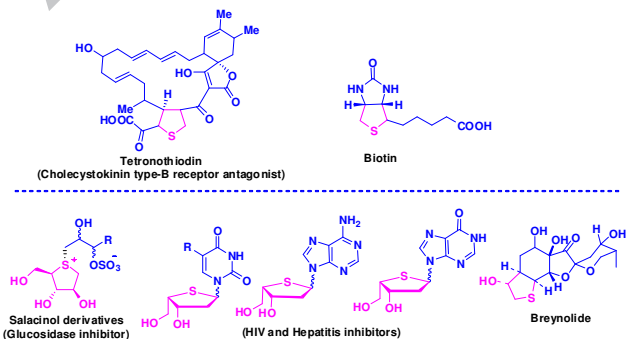


Figure-1: Biological active compounds with thiolane moiety

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 (**Figure-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]

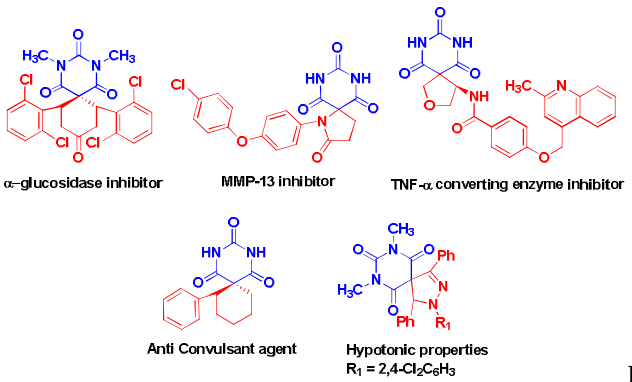


Figure-2: Biological active compounds with barbituric acid moiety

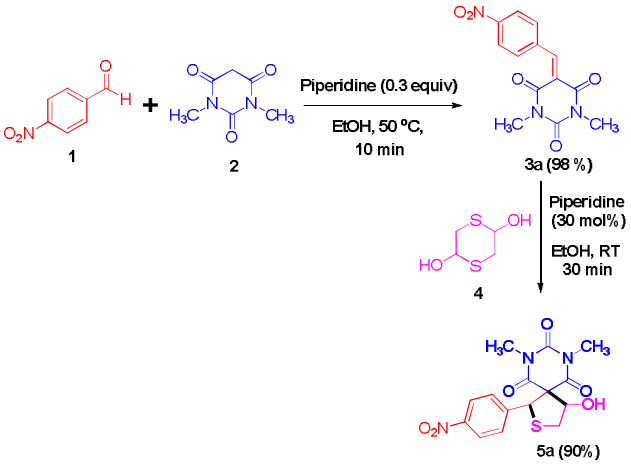
Most of the biochemical processes in living organisms are based on the water because of its unique properties. Whereas, in synthetic organic chemistry, water was a least preferred solvent because of its reactivity with some of the functional groups and the solubility problem of organic molecules. But 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 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.

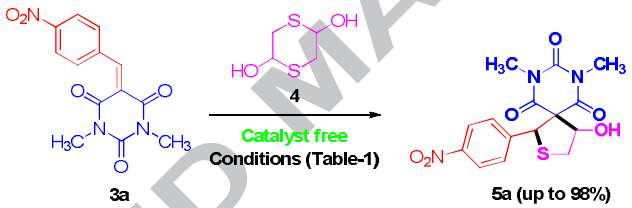
Keeping in view of above all, considering the medicinal importance of the spiro-barbiturates, tetrahydrothiophenes and quaternary centered molecules, and in continuation of our interest in environmental friendly green synthetic methods,[5c,25] we herein report a simple, straight forward and catalyst-free 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.

To achieve this, initially, the unsaturated system (**3a**) was generated by the reaction of 4-nitrobenzaldehyde (**1**) and barbituric acid (**2**), and reacted with 1,4-dithiane-2,5-diol (**4**) in presence of piperidine (30 mol%)[5c] to give the spiro-barbiturate-thiolane hybrid (**5a**) in 90% yield (two step sequence) (**Scheme 1**). The formation of the desired product was confirmed by ^{1}H, ^{13}C-NMR and mass spectral data.



Scheme-1. Sulfa-1,4-Michael followed by intramolecular Aldol reaction of barbituric acid olefin (two-step sequence)[5c]

After confirmation of the product, above reaction (**II step**) was performed without catalyst (piperidine) using different solvents [from non-polar to polar and aprotic to protic solvents] and the results are depicted in **Table-1**. From these experiments, it was observed that the polar protic solvents (MeOH, EtOH, and H_2O) are giving the desired product (**5a**) in 60-85% yield. Further, to find better reaction conditions, experiments were conducted by using water as solvent/promoter (***catalyst-free conditions***) with variation in the reaction concentration (from 5 mL to 2 mL; **Scheme 2**). It is noteworthy to mention that the reaction is working well at 0.086 M total reaction concentrations with 98% yield. The reactivity of water at particular concentrations could be attributed to its capacity to bring the reactant molecules by inducing the hydrogen bonding along with the hydrophobic behavior of organic molecules which may be helping to promote the reaction. This argument is well supported by the experiments using water:MeOH (1:1) and water: EtOH in (1:1), D_2O, brine, Ethylene glycol and PEG-400 as reaction medium (all at 0.086 M total reaction concentrations) where there is a possibility for partial hydrogen bonding or no hydrogen bonding (entries 16-21; **Table-1**).



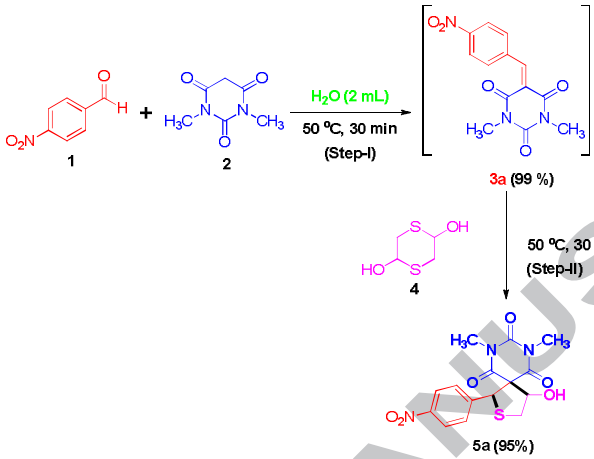
Scheme-2: Reaction of barbiturate olefin (**3a**) with 1,4-dithiane-2,5-diol (**4**) under catalyst-free conditions

Table-1: Optimization of the reaction conditions under **catalyst-free** conditions

S. No.	Solvent	Reaction time (h)	Isolated yields (%)[a]
1	Tetrahydrofuran	24	ND
2	Dioxane	24	ND
3	Dimethylsulfoxide	24	ND
4	N, N-Dimethylformamide	24	ND
5	Acetonitrile	24	ND
6	Chloroform	24	ND
7	Dichloromethane	24	ND
8	1,2-Dichloroethane	24	ND
9	MeOH (0.086 M)	10	60
10	EtOH (0.086 M)	10	65
11	Water (0.0345 M)	5	85
12	Water (0.0432 M)	5	90
13	**Water (0.086 M)**	**1**	**98**
14	Water (0.172 M)	5	95
15	Water (0.345 M)	5	90
16	Water:MeOH (1:1; 0.086 M)	4	75
17	Water:EtOH (1:1; 0.086 M)	3	75
18	D_2O (0.086 M)	24	Trace
19	Brine (0.086 M)	24	60
20	Ethylene glycol (0.086 M)	24	30
21	PEG-400 (0.086 M)	24	40

Table-1. Optimization of reaction conditions for Sulfa-1,4-Michael/intramolecular aldol reaction; [a]All the reactions were performed at 0.320 mmoles of barbiturate olefin (**3**)

After successful optimization of the reaction conditions (**catalyst-free**; **II step**), attempts were made for **one-pot**, **catalyst-free** synthesis of title compounds from corresponding aldehydes. Towards this, the reaction of *p*-nitrobenzaldehyde (**1**) and barbituric acid (**2**) at room temperature gave the intermediate (**3a**) in 4 h which was further converted into spiro thiolane (**5a**) in 30 min with 85% overall yield. To reduce the overall reaction time, the reactants in the first step were heated to 50 ^{o}C to give the intermediate (30 min, 99%) which was reacted with 1,4-dithiane-2,5-diol (**4**) at same temperature and stirred for 30 min to give the desired product in 95% yield (**Scheme 3**). Later, different substituted aldehydes with electron donating and withdrawing groups were reacted with barbituric acid (**2**) to give corresponding intermediates which on reaction with 1,4-dithiane-2,5-diol (**4**) gave the spiro-barbiturate-thiolane hybrids (**5b**-**5s**) in good yield. The **Figure-3** indicate that the aldehydes with electron donating groups require more time (over all reaction time) compare to the substrates with electron withdrawing groups for completion of the reaction. All the products were characterized using complementary spectral data (See ESI for ^{1}H-, ^{13}C-NMR and mass spectra).[26]



Scheme-3: One-pot Knoevenagel condensation followed by sulfa-1,4-Michael / intramolecular Aldol reaction of barbiturate olefins (optimized conditions)

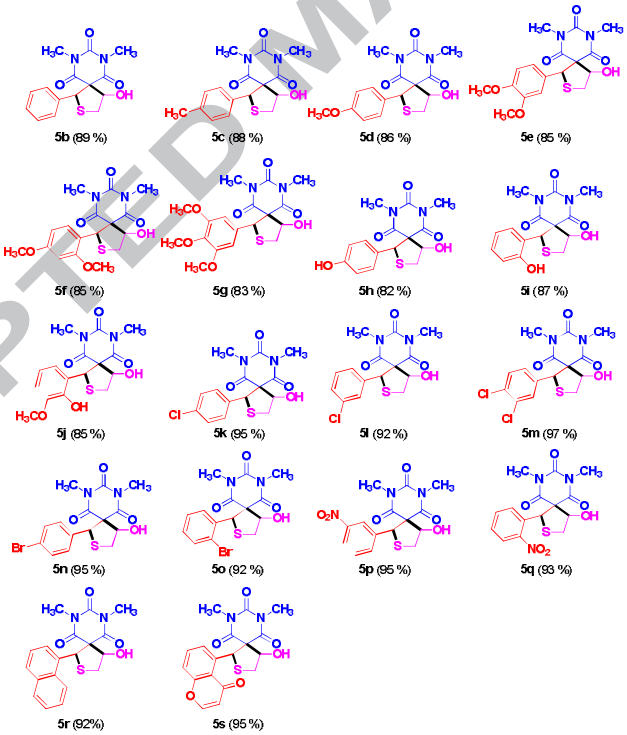
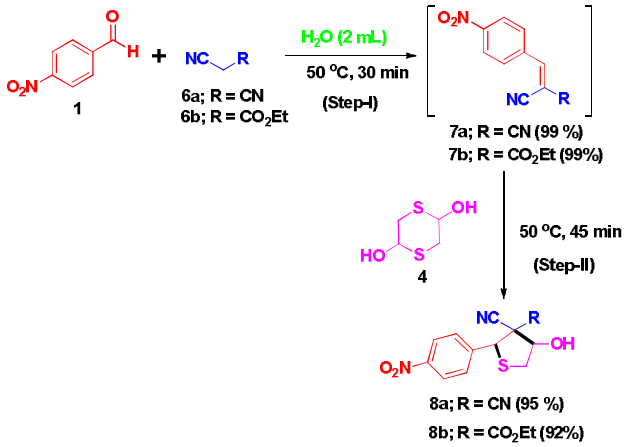


Figure-3. Spiro-barbiturate-tetrahydrothiophene derivatives (**5b-5s**)

After successful synthesis of a library of spiro-barbiturates, attention was shifted towards the synthesis of functionalized tetrahydrothiophenes with quaternary centers with geminal functional groups (electron withdrawing). To achieve this, various aldehydes were treated with malononitrile (**6a**)/ethyl cyanoacetate (**6b**) in water (2 mL) at 50 ^{o}C to give the olefinic system which was reacted with 1,4-ditiane-2,5-diol (**4**) to give the desired products (**8a-8r**) in 80-95% yields (**Scheme 4; Figure-4**). In this case, also the substrate dependent reactivity was observed for the aldehydes with electron donating and withdrawing groups as discussed earlier.



Scheme-4: One-pot Knoevenagel condensation followed by sulfa-1,4-Michael/intramolecular Aldol reaction of benzylidene malononitriles (**7a** and **7b**) under optimized conditions.

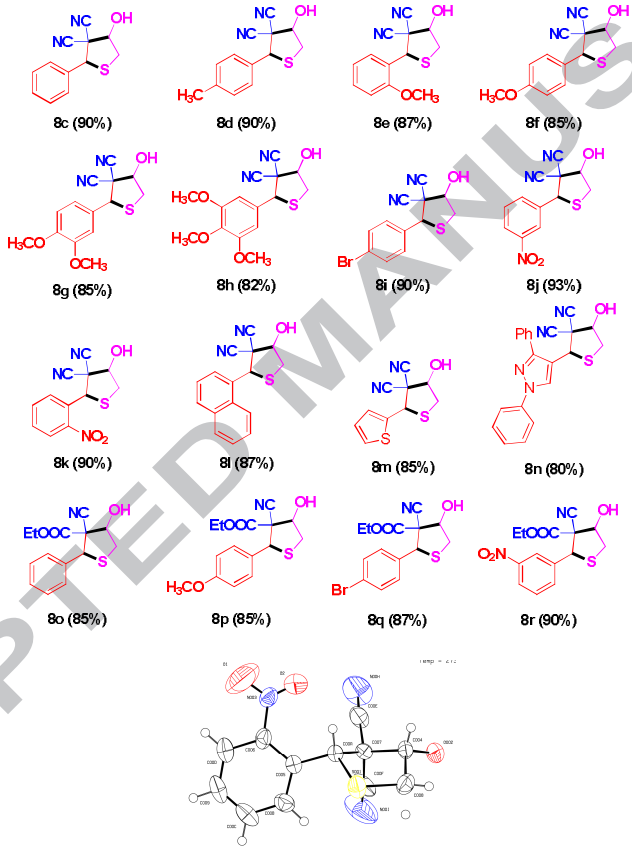


Figure-4: Functionalized quaternary centered tetrahydrothiophene derivatives (**8c**-**8r**) and ORTEP diagram of **8k** (CCDC 1545995).

From the transition states proposed, we assume that the insoluble starting materials are aggregating because of their hydrophobic interactions with hydrogen-bonded water network. These non-covalent interactions are helping in bringing reactive partners together to give Knoevenagel condensation product which will again react with the *in situ* generated monomeric mercaptaldehyde (**4**) by forming active transition state which is facilitating the sulfa-1,4-Michael followed by intramolecular Aldol reactions to give the final thiolanes as shown in **Figure 5**.

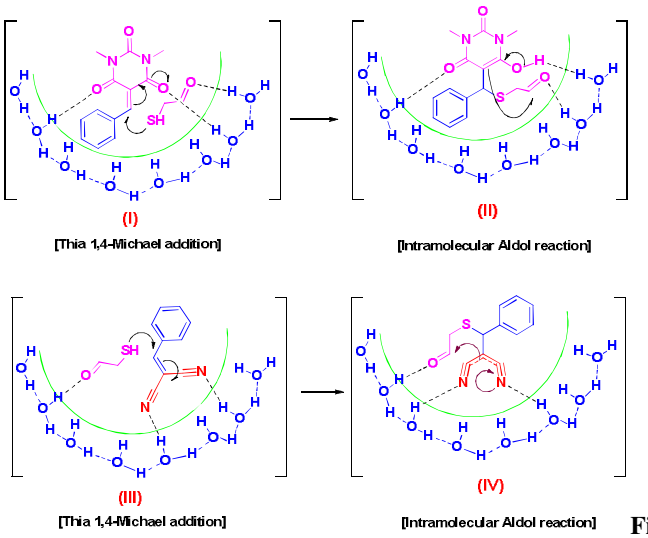


Figure-5: Possible transition states for sulfa-1,4-Michael / intramolecular aldol reactions of 1,4-dithiane-2,5-diol and 2-benzylidenemalononitrile and barbiturate olefins.

In conclusion, we have demonstrated successful synthesis of the spiro-barbiturate-thiolane hybrids and quaternary centered tetrahydrothiophene derivatives under green and catalyst free conditions. The aqueous conditions, one-pot approach, high yields, broad substrate scope are advantages of this method. Further synthetic applications and biological studies are in progress and will be published elsewhere. Further functionalization of the resulting products is in progress in our laboratory.

Acknowledgments

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[§]Supporting information available

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26. ***General Procedure for the One-pot synthesis of thiolanes****:* A mixture of aldehyde (1 Equiv) and malononitrile / barbituric acid (1 Equiv) in water (2 mL; total reaction concentration 0.086 M) was heated at 50 ^{o}C for 30 min. After the formation of intermediate (olefin), 1,4-dithiane-2,5-diol (0.75 Equiv) was added at same temperature and heating continued until the completion of the reaction (monitored by TLC). Then the reaction mixture was extracted EtOAc (20 X 2 mL). The combined organic layers were dried using sodium sulfate and concentrated under reduced pressure to give the crude product which was purified by column chromatography. Purification using petroleum ether-EtOAc gave the desired product. *Representative analytical data of 4-hydroxy-7,9-dimethyl-1-(4-nitrophenyl)-2-thia-7,9-diazaspiro[4.5]decane-6,8,10-trione* ***(5a):*** Yield = 95% (White solid); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.14 (d, J = 8.7 Hz, 2H), 7.52 (d, J = 8.6 Hz, 2H), 5.33 (s, 1H), 5.25 (s, 1H), 3.76 (t, J = 9.8 Hz, 1H), 3.39 (t, J = 9.8 Hz, 1H), 3.32 (s, 3H), 2.99 (s, 3H). ^{13}C-NMR (101 MHz, $CDCl_3$): δ 169.03, 165.09, 149.98, 148.09, 142.48, 129.40, 123.70, 82.20, 67.44, 54.81, 36.47, 29.40, 28.33. Mass (ESI-MS): Calculated for $C_{15}H_{15}N_3O_6S$, m/z: 365; found: 364 (M-1) [please see the electronic supporting information for spectral data other compounds].

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

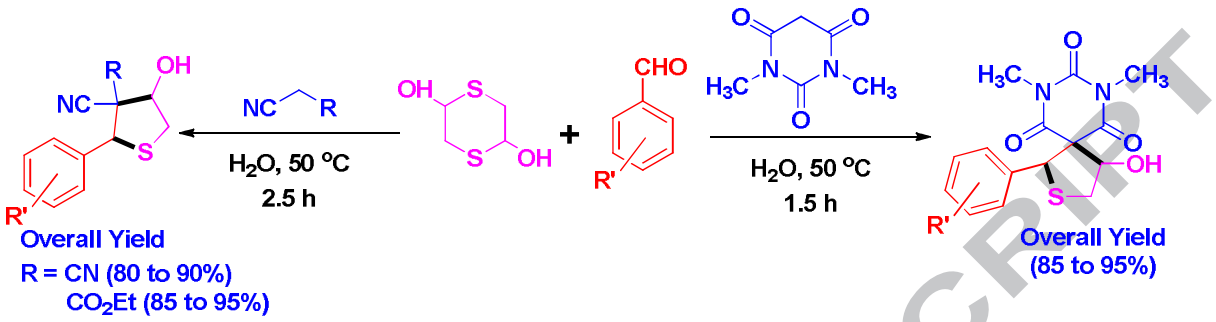
Sakkani Nagaraju, Kota Sathish, Banoth Paplal and Dhurke Kashinath*

Highlights:

1. Use of “On-water" concept for tetrahydrothiophene synthesis
2. Catalyst-free protocol for the spiro-barbiturates
3. Consecutive/one-pot sequence for Knoevenagel, thia-Michael and Aldol reactions
4. Simple procedure for the all carbon quaternary cantered molecules

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

Sakkani Nagaraju, Kota Sathish, Banoth Paplal and Dhurke Kashinath*



27.