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Imposed hydrophobic interactions by NaCl: Accountable attribute for the synthesis of spiro[acenaphthylene-1,5′-pyrrolo[1,2-*c*]thiazole] derivatives *via* 1,3-dipolar cycloaddition reaction in aqueous medium

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ABSTRACT

We have described herein the significance of hydrophobicity for the synthesis of spiro[acenaphthylene-1,5′-pyrrolo[1,2-*c*]thiazole] derivatives through 1,3-dipolar cycloaddition reaction of acenaphthenequinone, 1,3-thiazole-4-carboxylic acid and Knoevenagel adduct in aqueous medium. The reaction was dramatically influenced by the presence of NaCl. In water alone, no reaction commencement was observed due to the low magnitude of hydrophobic effect. However, addition of NaCl augments the hydrophobic effect of water, which was actually found to impel the reaction by a notable magnitude and produced desired product in high yield with excellent regio- and stereo selectivity. This imposed hydrophobic effect by NaCl is the deciding factor for making the new water-assisted strategy. To the best of our knowledge, this is a first report of 1,3-dipolar cycloaddition reaction of azomethine ylides with olefins representatives in aqueous medium. This process is capable of generating four chiral centers comprising one spiro center with two C-C, one C-N bonds in a single reaction which enhances the biocidal profile or may discover new medicinal properties. Amputation of conventional organic solvents and toxic reagents, high atom-economy, mild reaction conditions, waste free synthesis and formation of water and carbon dioxide as the only by-product are additional advantages of the present methodology relevant to green chemistry.

KEYWORDS: Hydrophobic interactions, Aqueous Chemistry, NaCl, Salting-out effect, Regio- and stereo selectivity.

1. INTODUCTION

Cycloaddition reactions have been widely investigated as an important bond forming reaction. In particular, the 1,3-dipolar cycloadditions have attracted a fair interest because it constitutes an important class of substances especially substituted pyrrolidine, pyrrolizidine and thiazolidine rings with highly pronounced biological activities[1]. In this regard, spiropyrrolidine and their

derivatives have attracted meticulous attention as they have served as useful synthetic intermediates[2] and also act as antiviral, antitumoral, antibiotic agents, local aneasthetics, and inhibitors of human NK-1 receptor, etc. and also been found in a fascinating array of bioactive natural products[3] (Fig. 1).

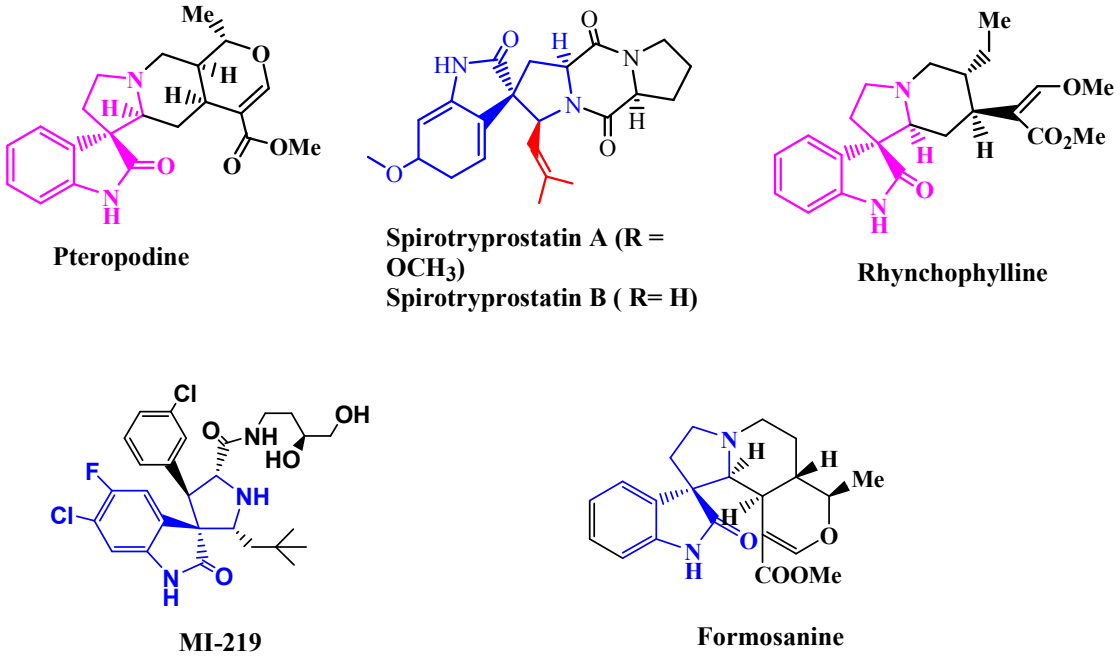


Fig. 1 Spiropyrrolidine -type natural products and drugs

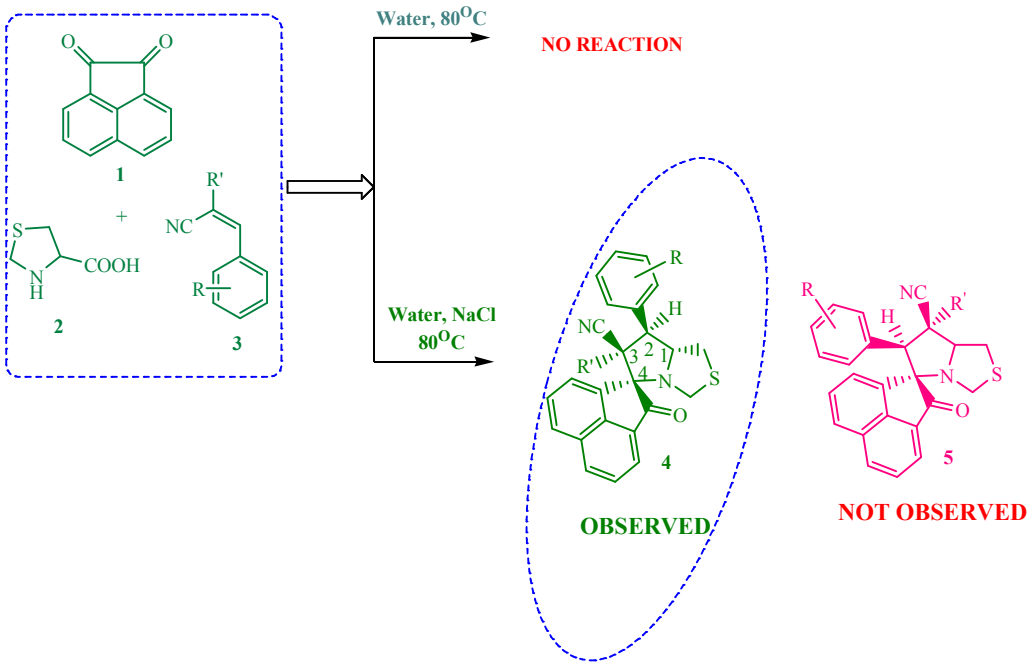
Thus, the potentialities of these compounds have led them being encountered through the development of 1,3-dipolar cycloaddition reaction of azomethine ylides with olefins representatives, since it offers high regio- and stereoselective results[4]. However, a watchful study described that most of the methodologies suffer some inadequacy owing to their limited utility, use of acid catalyst, hazardous reagents, volatile organic solvents and also there is often no recovery of catalyst[5]. Moreover, the use of volatile organic solvents is not so good which adversely affects the economic as well as the ecofriendly nature of these reported methodologies. While, decisive amendments have been documented by using ionic liquid,[6] but it involves tedious preparation methods. Moreover, their environmental safety is still arguable due to their corrosive, non bio-degradable and toxic nature.[7]

Organic reactions in water without use of any detrimental organic solvents are of immense interest[8]. Due to its high heat capacity and unique redox stability, water is by far one of the safest

mediums to carry out organic reactions particularly the exothermic ones[9]. When water is used as a reaction medium, it leads to some specific interactions like polarity, hydrogen bonding, hydrophobic effect and trans-phase interactions, etc. due to its exclusive structure and incredible physical and chemical assets. These interactions influence the reaction course to a great extent[10]. Thus, attainment of sustainable synthetic strategy has inherently involves implementation of developed processes in water to accomplish greener syntheses. However, the insolubility of most of the organic reactants in water makes the reaction mixtures heterogeneous which proves to be the major difficulty while using water as a solvent. But the effect of water on the heterogeneous reactions is precisely opposite. Actually, depending on the nature of the reaction, water was observed to accelerate most of the reactions appreciably on its interface. The observed rate enhancement in water was explained by the hydrophobic effect[11].

In the above regards, we have focused on sustainable synthetic practices that rely on a few virtually ideal reaction types[12]. In the succession of this work, we have illustrated that many such reactions frequently proceed optimally in water[13], and mostly when the organic reactants are insoluble in the aqueous phase[14]. Recently, we have used an idea by proposing NaCl promotes the reaction that actually requires no catalyst in aqueous medium due to its salting out effect[15]. In the past, salt effects have also been employed as synthetic/mechanistic tools for various aqueous reactions[11b,16]. As compared to others NaCl is very cheap, easily available, harmless and most accessible salting out agent.

To the best of our knowledge, there is no report on 1,3-dipolar cycloaddition reaction of azomethine ylides with olefins representatives in aqueous medium. In continuation of our ongoing program for the development of sustainable processes[17] and our expertise in 1,3-dipolar cycloaddition reactions[18], herein, we wish to report for the first time the role of NaCl for the facile and efficient synthesis of spiro[acenaphthylene-1,5′-pyrrolo[1,2-*c*]thiazole] derivatives (**4a-u**), in a highly regio- and stereoselective manner through 1,3-dipolar cycloaddition reaction of acenaphthenequinone (**1**), 1,3-thiazole-4-carboxylic acid (**2**) and Knoevenagel adduct (**3**) in aqueous medium (Scheme 1).

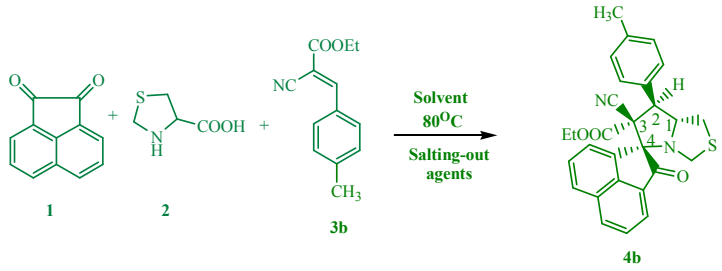


Scheme 1. Synthesis of spiro[acenaphthylene-1,5′-pyrrolo[1,2-*c*]thiazole] derivatives

2. RESULTS AND DISCUSSION

To investigate the feasibility of the "Aqueous route" for the 1,3-dipolar cycloaddition reaction, a succession of trials was carried out using acenaphthenequinone (**1**), 1,3-thiazole-4-carboxylic acid (**2**) and Knoevenagel adduct (**3b**) as a model reaction under various solvents in the absence of NaCl. When the reaction was performed in organic solvents moderate yield of the product (4b) was obtained (Table 1, entries- 1 and 2). In contrast, in sustainable solvents like PEG, EG, Water, reaction did not precedes and no product formation was observed (Table 1, entries -3, 4 and 5). However, in the presence of NaCl the reaction proceeded smoothly to afford the corresponding product in high yield in aqueous media. Thus, the presence of NaCl in heterogeneous reaction made significant difference. The presence of NaCl leads to a decrease in the solubility of the reactants as compared to that in water alone. The heterogeneous aqueous reaction systems underline the importance of hydrophobic interactions in rationalizing the effect of water on 1,3-dipolar cycloaddition reaction. In case of water alone (Table 1, entry-5), the magnitude of hydrophobic effect was less and not sufficient for reaction commencement. While the product formation in presence of NaCl under aqueous medium is due to its salting-out effect. Further, in all cases (expect entry 3-5) single diastereomer was obtained as final product.

Table 1. Effect of solvent and different salting-out agents for the synthesis of compound **4b**[a]



Entry	Solvent	Salting-out agent[@]	Time	Yield(%)*
1	Methanol	-	2 h	55
2	Toluene	-	2 h	30
3	Polyethylene glycol	-	2 h	No reaction
4	Ethylene glycol	-	2 h	No reaction
5	Tap water	-	2 h	No reaction
6	Tap water	NaCl	40 min	93
7	Tap water	KCl	40 min	78
8	Tap water	NaBr	40 min	62
9	Tap water	CH_3COONa	40 min	41
10	Tap water	NH_4Cl	40 min	68
11	Tap water	Na_2SO_4	40 min	57
12	Tap water	$MgSO_4$	40 min	51
13	Tap water	SDS	2 h	30
14	Tap water	CTAB	2 h	32
15	Distilled water	NaCl	40 min	93
16	Mili Q water	NaCl	40 min	93
17	D_2O water	NaCl	40 min	71
18	Neat	NaCl	6 h	28
19	MeOH/H_2O (3:1, homogeneous)	-	40 min	52

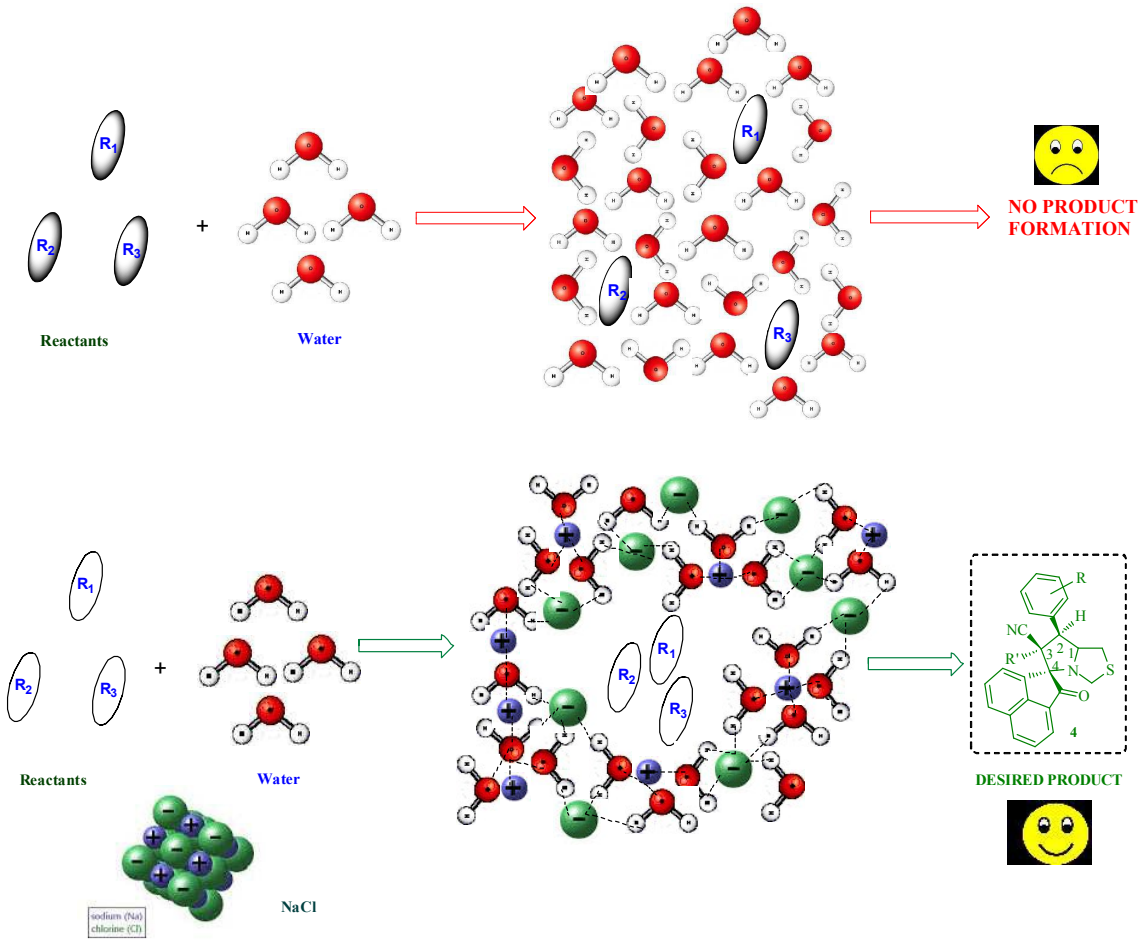
[a]Reactions are performed on a 1:1:1 ratio of reactants in various solvent and different salting-out agents at 80 °C.
[@] 10 mol % salting-out agent
* Isolated yield

In order to evaluate the efficiency of the protocol, a comparison of efficiency of NaCl with several other salting out agents is presented in Table 1 (Entries- 7-12). These results show that NaCl is superior to the others in terms of yield and reaction time. As compared to the others, NaCl in aqueous solutions increase the hydrophobic effect of water toward the reactants due to its predominant salting out effect[19,20]. Further, with micellar SDS and CTAB solutions the yields of desired product were poorer (Table 1, Entry 13-14). Probably, it is a result of the fact that the purely hydrocarbon diene prefers the interior of the micelles, whereas the more polar dienophile

resides on average in the headgroup region of the aggregates. This spatial separation results in a modest inhibition of the reaction[21].

To find out if water provides an advantage over the neat condition, the progress of the reaction under solvent-free conditions was monitored. Under aqueous medium, the reaction is completed within 40 minutes at 80 °C. The corresponding neat reaction takes virtually several hours and gave inadequate result, which shows that the rate hastening is not the sole consequence of an increase in the effective concentration of reactants (Table 1, entry-18). As analogous outcomes were obtained in tap, distilled and MQ (Milli-Q) water, (Table 1, entries - 6, 15 and 16) the reactions were carried out in tap water so that the efforts and the expenditure of energy required to purification of water are avoided. In general, the product is isolated in pure form simply by filtration and did not require additional efforts at purification. Where required, the purification was achieved by crystallization. To make sure that any metal ion leaching out from the glass vessel did not afford catalytic assistance, the reaction was also carried out in a plastic vessel in water and the corresponding product was obtained in 93% yield. The reaction slowed noticeably when D_2O was used in place of water (Table 1, entries - 6 and 17). NaCl is less soluble in heavy water (D_2O) as compared to H_2O due to isotope effect.

When NaCl dissolve in water, there is a volume contraction, electrostriction, as water collapses around the ions to enhance the structuring of aqueous phases around them due to their strong interactions with water dipoles[22]. The solubility of reactants with significant hydrophobic surfaces is decreased by the addition of a small amount of NaCl. This can be thought as the energy cost producing a reactants-sized hole in the solvent. As the consequence, reactant–reactant interactions are stronger than the solvent–reactant interactions; the reactant molecules react easily with the help of hydrophobic interactions. This unique type of hydrophobic interactions is best attributed as imposed hydrophobic interactions[23] (Scheme 2**)**. In this case, the imposed hydrophobic interactions are actually found to ‘‘actuate’’ the reactions by a notable magnitude.



Scheme 2. Role of NaCl in heterogeneous aqueous reaction systems

Since the reactants are not soluble in aqueous medium, the reaction can take place at the organic-aqueous interface. In order to understand this aspect, we carried out the reaction in homogeneous as well as heterogeneous system. Methanol was used to make the reaction homogeneous in water. Under identical condition, higher conversion of the reactants into the product was observed in heterogeneous as compared to homogeneous conditions (Table 1, entries - 6 and 19).

Moreover the effect of temperature was also studied (Table 2). On low temperature solvolysis process of NaCl was slow. This may lead to weaker hydrophobic effect provided to the reaction. Hence, lower yield of the product was observed at lower temperature. At the elevated temperature, the reaction goes faster in the presence of the NaCl because of the rise in the temperature accelerated solvolysis[24] process of NaCl, which also increases the hydrophobic effect of water therefore increased reaction rate was observed. In evaluating the effects of NaCl concentration, the best yields were found in the presence of 10 mol% NaCl. A higher amount of NaCl did not improve the results to an appreciable extent (Table 2).

Table 2. Effect of NaCl concentration and temperature for the synthesis of compound **4b** [a]

Entry	NaCl Concentration	Temperature	Yield (%)*	Time
1	10 mol %	RT	20	24 h
2	10 mol %	50 °C	62	4 h
3	10 mol %	80 °C	93	40 min
4	10 mol %	90 °C	93	40 min
5	5 mol %	80 °C	58	40 min
6	15 mol %	80 °C	93	40 min

[a]Reactions are performed on a 1:1:1 ratio of reactants in water.
* Isolated yield

With the optimal conditions in hand, next we examined the scope of the reaction with respect to Knoevenagel adduct precursors (dipolarophile) under the optimized conditions. The results are summarized in Table 3. High endo-selectivity of products **(4a-u)** was obtained virtually independent of stereo and electronic properties of substituents; electron-withdrawing and donating group almost did not affect the endo and regioselectivity of the product. The only byproducts of these cycloadditions are water and carbon dioxide.

Table 3. Synthetic results of spiro[acenaphthylene-1,5′-pyrrolo[1,2-*c*]thiazole] derivatives **4a-u**

Entry	Product	R	R′	Time (min)	Yield[a] (%)
1	4a	H	COOEt	30	92
2	4b	4-CH_3	COOEt	40	93
3	4c	4-F	COOEt	32	90
4	4d	2,4-diCl	COOEt	38	89
5	4e	4-NO_2	COOEt	40	92
6	4f	4-Cl	COOEt	35	91
7	4g	3,4-diCl	COOEt	40	90
8	4h	4-Br	COOEt	36	88
9	4i	Thiophene	COOEt	33	92

10	4j	3,4-diOCH_3	COOEt	38	90
11	4k	H	$CONH_2$	30	89
12	4l	4-CH_3	$CONH_2$	33	87
13	4m	4-F	$CONH_2$	40	90
14	4n	2,4-diCl	$CONH_2$	35	88
15	4o	4-NO_2	$CONH_2$	40	91
16	4p	4-Cl	$CONH_2$	38	92
17	4q	3,4-diCl	$CONH_2$	37	89
18	4r	4-Br	$CONH_2$	35	90
19	4s	Thiophene	$CONH_2$	40	88
20	4t	4-CH_2CH_3	$CONH_2$	32	91
21	4u	4-$CH_2CH_2CH_3$	$CONH_2$	40	89

[a] Isolated yield

Encouraged by the above interesting results, we also attempted the reaction of isatin, 1,3-thiazole-4-carboxylic acid and Knoevenagel adduct to further broaden the scope of this three component reaction in the same conditions. But unfortunately, reaction didn't proceed to formed corresponding spiro[indoline -1,5′-pyrrolo[1,2-*c*]thiazole]. On the basis of the results obtained above, we assume that the imposed hydrophobic effect by NaCl+water system doesn't create a sufficient space for the reaction due to the low hydrophobic surface of isatin as compared to acenaphthenequinone. The application of this new NaCl+water mediated protocol for 1,3-dipolar cycloaddition reaction of various azomethine ylides with different olefins representatives will be further expanded. This work is under way in our laboratory and will be reported in due course.

The structure of novel spiro[acenaphthylene-1,5′-pyrrolo[1,2-*c*]thiazole] derivatives obtained by 1,3-dipolar cycloaddition of azomethine ylide was elucidated with the help of IR, ^{1}H NMR, ^{13}C NMR and mass data as illustrated for compound **4b**. In the IR spectrum, sharp peak appeared at 1732 and 1758 corresponds to C=O stretching for acenaphthenequinone and ester carbonyls

respectively and the peak at 2242 cm^{-1} corresponds to C≡N stretching of the product **4b.** In the ^{1}H NMR spectrum of **4b**, peaks in the range of δ 7.27–8.43 ppm show aromatic protons. The N–CH proton in thiapyrrolizidine ring was seen as multiplate at δ 4.34-4.39 ppm and the benzylic proton appeared at δ 3.95 ppm as a doublet. The O–CH_2 proton was seen as multiplate at δ 3.65-3.68 ppm. Peaks at 3.51 ppm as doublet and 3.19-3.40 ppm as multiplate for two CH protons of CH_2 linked with nitrogen and sulphur atoms and another CH_2 proton appeared at δ 2.05-2.55 ppm as a multiplet, which explained the regiochemistry of the cycloadduct. In contrast, if the other regioisomer had been formed, the benzylic proton would have appeared as a singlet instead of triplet in the ^{1}H NMR spectrum. In the ^{13}C NMR, the peak at δ 78.14 ppm corresponds to one spiro carbons and peaks at δ 162.99 and 202.93 ppm show the presence of two carbonyl carbon. A distinguishing peak observed at m/z: 468 in the mass spectrum for [M^{+}] ion further conforms the product **4b**.

Study of reaction kinetics:

Kinetic study of the model reaction of acenaphthenequinone (**1**), 1,3-thiazoles-4-carboxylic acid (**2**) and Knoevenagel adduct (**3b**) in the presence NaCl was investigated by UV/Vis analyses. In order to find out the suitable wavelength for the kinetic study of the reaction, firstly, the UV-Vis spectra of 10^{-2} M solution of each reactant **1**, **2**, **3b** and NaCl (prepared in a 50 : 50 mixture of water and ethanol) were recorded over the wavelength range 200-500 nm. Fig. 2-5 represents the obtained spectra of the reactant **1**, **2**, and **3b** and NaCl, respectively.

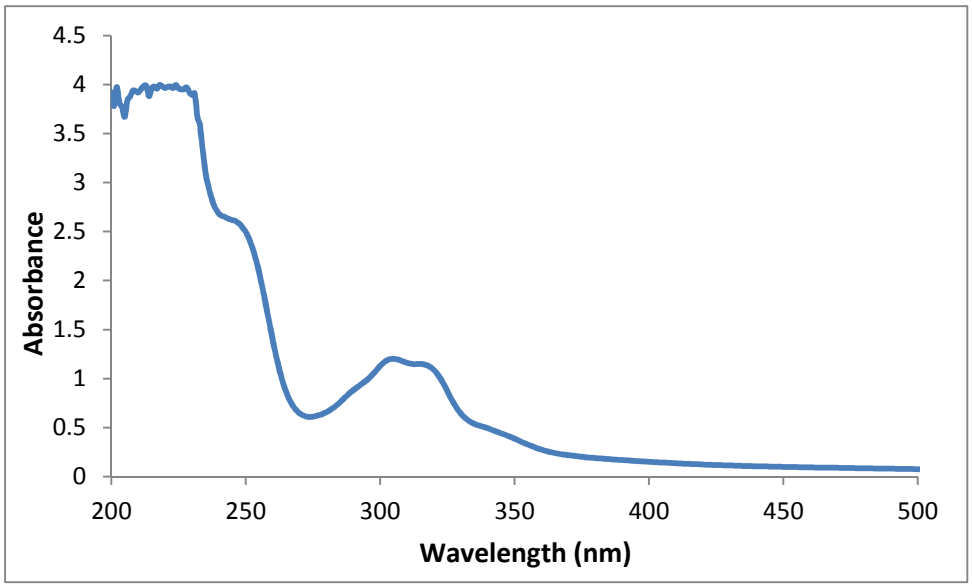


Fig. 2 The UV-Vis spectrum of 10^{-2} M acenaphthenequinone solution

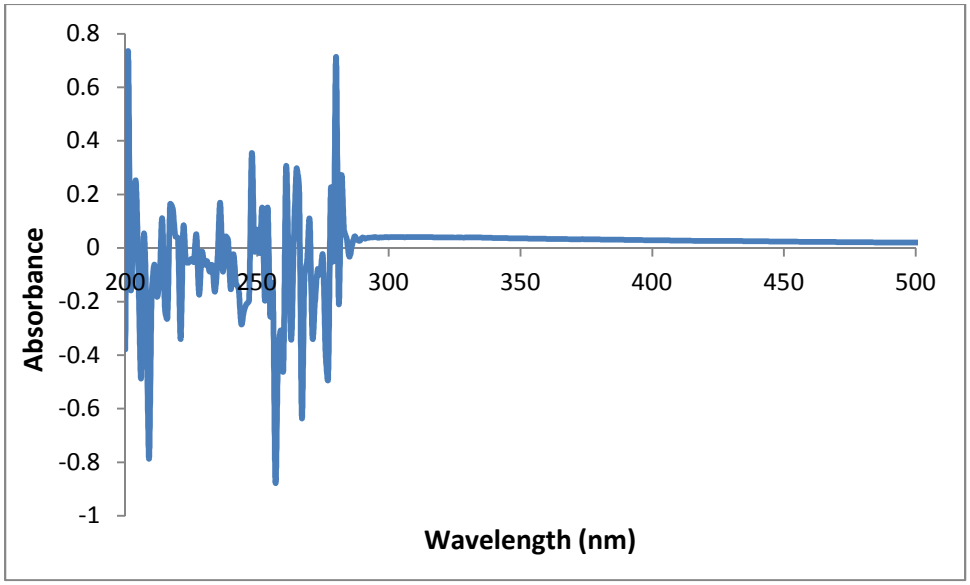


Fig. 3 The UV-Vis spectrum of 10^{-2} M 1,3-thiazoles-4-carboxylic acid solution

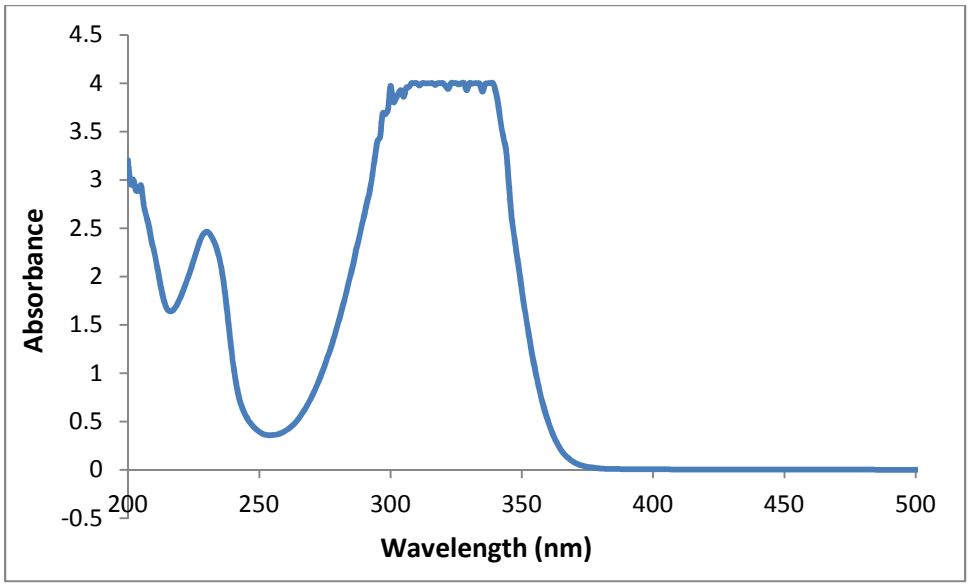


Fig. 4 The UV-Vis spectrum of 10^{-2} M Knoevenagel adduct (3b) solution

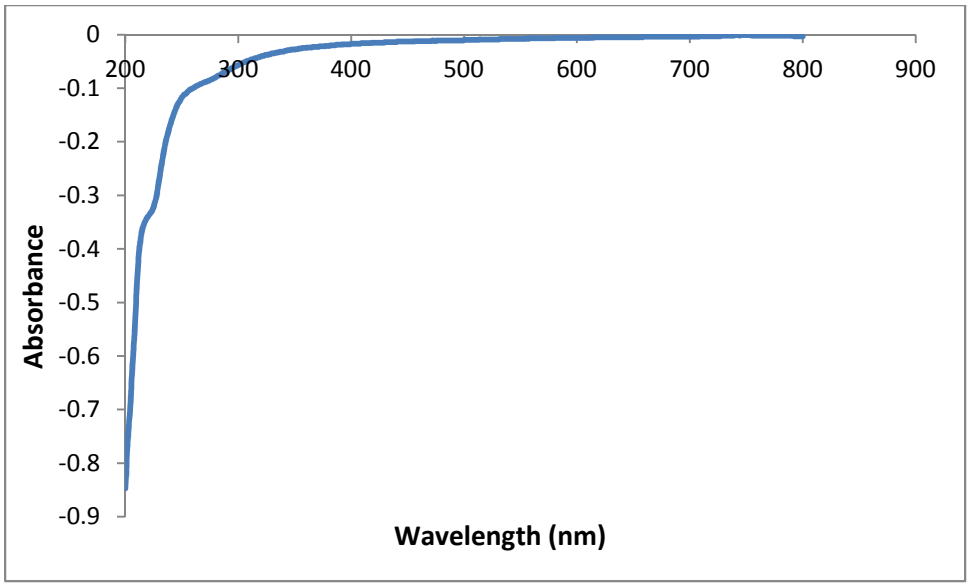


Fig. 5 The UV-Vis spectrum of 10^{-2} M NaCl solution

In further experiments, the reaction mixture was examined under UV-Vis analysis by starting the model reaction with a 10^{-2} M solution of each reactant (**1**, **2**, and **3b**) and 10^{-2} M NaCl solution. The reaction was examined at every 1 min. time interval. From this experiment, the appropriate wavelength was discovered to be 345, 350, and 355 nm. At these wavelengths, all the reactants and NaCl have comparatively no absorbance value. These analytical results guided us to perform the kinetics and mechanistic investigation of the reaction at these wavelengths.

In order to obtain a partial order of reaction with respect to each reactant **1**, **2** and **3b** pseudoorder conditions were performed for the reaction. Thus, in the next experiment, the reaction of 10^{-3} M acenaphthenequinone **1**, 10^{-2} M 1,3-thiazoles-4-carboxylic acid **2**, and 10^{-2} M Knoevenagel adduct **3b** was performed in the presence of 10^{-2} M NaCl and kinetic study was done by plotting the UV/Vis absorbance versus time at wavelength 350 nm. The rate law can be expressed as-

$$\text{Rate} = k_{ovr}\,[\mathbf{1}]^x[\mathbf{2}]^y[\mathbf{3b}]^z[\text{Cat}]$$

$$\text{Rate} = k_{obs}\,[\mathbf{1}]^x$$

$$k_{obs} = k_{ovr}[\mathbf{2}]^y[\mathbf{3b}]^z[\text{Cat}] \qquad \text{(I)}$$

The zero, first or second order curve fittings can be drawn for the reaction with respect to the experimental value using the software associated with the UV/Vis instrument. From this study, a typical first pseudoorder experimental curve was obtained (Fig. 6). It was concluded that the reaction is of first order type with respect to acenaphthenequinone **1** ($x = 1$).

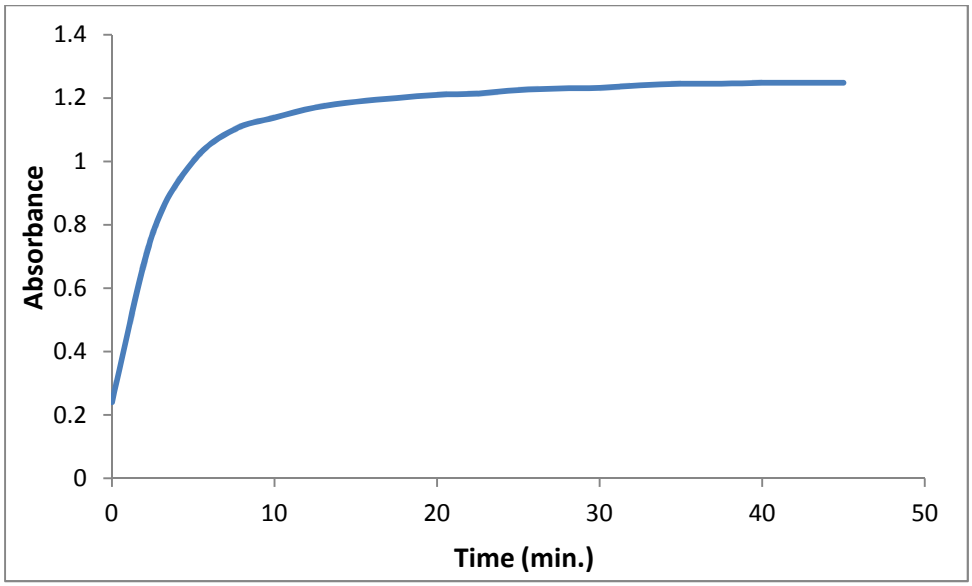


Fig. 6 Pseudo first order experimental curve in relation to acenaphthenequinone 1 (10^{-3} M) for the reaction among acenaphthenequinone 1 (10^{-3} M), 1,3-thiazoles-4-carboxylic acid 2 (10^{-2} M) and Knoevenagel adduct 3b (10^{-2} M) in a mixture of water and ethanol (50:50) at 350 nm.

Further, to obtain a partial order of reaction with respect to 1,3-thiazoles-4-carboxylic acid **2**, similar experiment was performed and reactant **2** was taken under pseudoorder condition (10^{-3} M of **2**) and reactants **1** acenaphthenequinone and **3b** Knoevenagel adduct were taken in excess (10^{-2} M). The rate law can be written as-

$$\text{Rate} = k_{ovr}\,[\mathbf{1}]^x[\mathbf{2}]^y[\mathbf{3b}]^z[\text{Cat}] \text{ or Rate} = k_{obs}\,[\mathbf{2}]^y$$

$$k_{obs} = k_{ovr}\,[\mathbf{1}]^x[\mathbf{3b}]^z[\text{Cat}] \qquad \text{(II)}$$

From the UV-Vis study a typical first order curve was obtained (Fig. 7). Therefore, it can be concluded that the reaction is of first order in relation to 1,3-thiazoles-4-carboxylic acid **2** (y = 1).

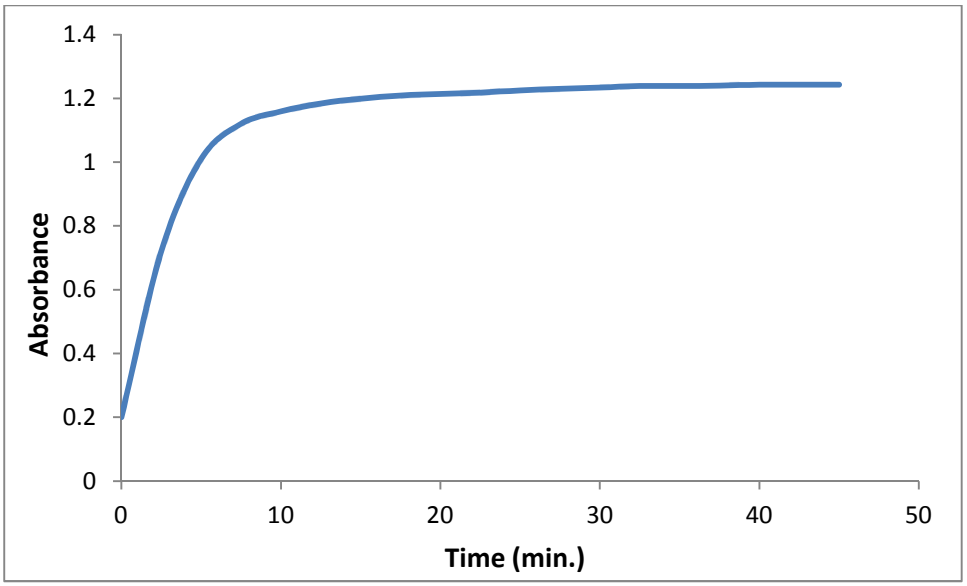


Fig. 7 Pseudo first order experimental curve in relation to 1,3-thiazoles-4-carboxylic acid 2 (10^{-3} M) for the reaction among acenaphthenequinone 1 (10^{-2} M), 1,3-thiazoles-4-carboxylic acid 2 (10^{-3} M) and Knoevenagel adduct 3b (10^{-2} M) in a mixture of water and ethanol (50:50) at 350 nm.

Further, the reaction was performed with an excess of acenaphthenequinone **1** and 1,3-thiazoles-4-carboxylic acid **2** (10^{-2} M of each) along with 10^{-3} M of Knoevenagel adduct **3b**. Here, the rate law can be expressed as-

$$\text{Rate} = k_{ovr}\,[\mathbf{1}]^{x}[\mathbf{2}]^{y}[\mathbf{3b}]^{z}[\text{Cat}]$$

$$\text{Rate} = k_{obs}\,[\mathbf{3b}]^{z}$$

$$k_{obs} = k_{ovr}\,[\mathbf{1}]^{x}[\mathbf{2}]^{y}[\text{Cat}] \qquad \text{(III)}$$

The experimental absorbance curve versus times was recorded for the above experiment at wavelength 350 nm. It gives a typical second order curve (Fig. 8). Then, the rate constant (k = 79.45 $\text{min}^{-1}\cdot\text{M}^{-1}$) of the reaction was automatically obtained from the software program.

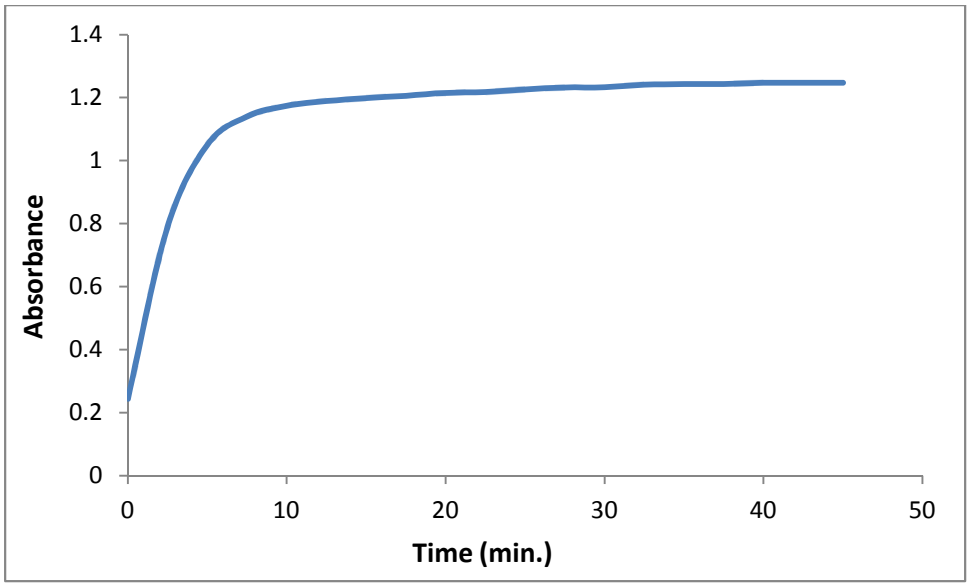


Fig. 8 Pseudo second order experimental curve in relation to Knoevenagel adduct 3b (10^{-3} M) for the reaction among acenaphthenequinone 1 (10^{-2} M), 1,3-thiazoles-4-carboxylic acid 2 (10^{-2} M) and Knoevenagel adduct 3b (10^{-3} M) in a mixture of water and ethanol (50:50) at 350 nm.

Further, the experimental absorbance curve was recorded versus time at wavelength 350 nm for the reaction mixture having same concentration of each reactant **1**, **2** and **3b** (10^{-2} M). This is shown in Fig. 9 which exactly fits to second order fitting curve. In this case, overall order of the reaction can be written as $x + y + z = 2$ for the rate law-

$$\text{Rate} = k_{ovr}\,[\mathbf{1}]^{x}[\mathbf{2}]^{y}[\mathbf{3b}]^{z}[\text{Cat}] \qquad \text{(IV)}$$

Then, the second order the rate constant (79.98 $\text{min}^{-1}\cdot\text{M}^{-1}$) of the reaction was automatically calculated by the software associated within the UV/Vis equipment.

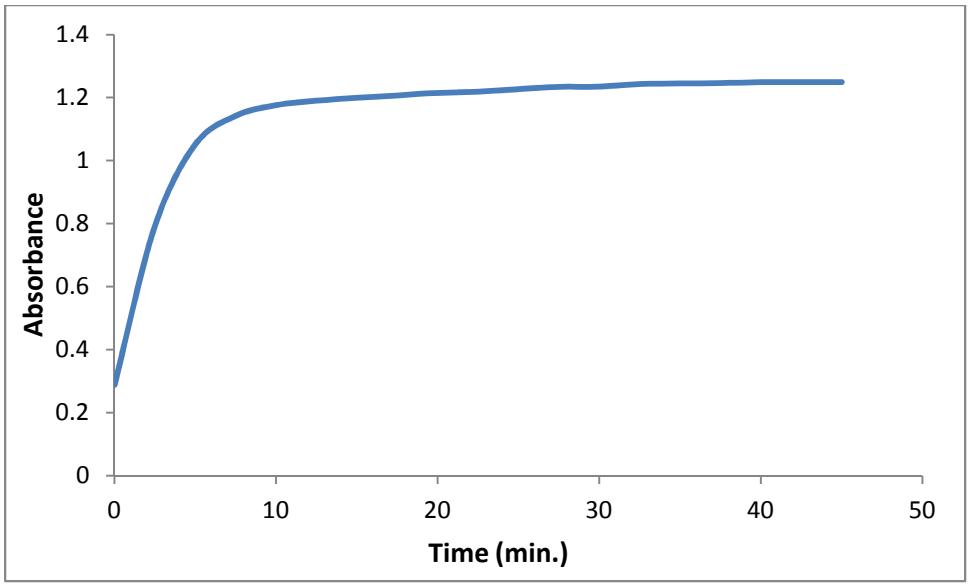


Fig. 9 Experimental absorbance change against time for the reaction among acenaphthenequinone 1 (10^{-2} M), 1,3-thiazoles-4-carboxylic acid 2 (10^{-2} M) and Knoevenagel adduct 3b (10^{-2} M) in a mixture of water and ethanol (50:50) at 350 nm.

The values of the rate constant were almost similar for both the experiments (Fig. 8; where the concentration of reactant **1** and **2** were taken in excess and Fig. 9; where concentration of each compound was same corresponding to 10^{-2} M). This is possible only when z is zero in both equations (III) and (IV). It means that the reaction is of zero and second order type in relation to compound **3b** ($z = 0$) and sum of **1** and **2** ($x + y = 2$), respectively. As a result, it can be concluded that the overall order of reaction is two.

Having the above analytical results in hand, the simplified scheme of the proposed reaction mechanism may be derived as follows (Scheme 3).

$$R_1 + R_2 + R_3 + C \xrightarrow{\text{Water}} P + C$$

$$R_1 + R_2 + C \xrightarrow{K_1} I_1 + C$$

$$I_1 + C \xrightarrow{K_2} I_2 + C$$

$$I_2 + R_3 + C \xrightarrow{K_3} P + C$$

R_1 = Acenaphthenequinone
R_2 = 1,3-thiazole-4-carboxylic acid
R_3 = Knoevenagel adduct
C = Catalyst (NaCl)
I_1 = Intermediate 1
I_2 = Intermediate 2
P = Product

Scheme 3: Simplified scheme of the proposed reaction mechanism

To investigate which step of the proposed mechanism is the rate-determining step, the rate law was written using the final step of reaction presented in simplified scheme.

$$\text{Rate} = K_3[I_2][R_3][C] \ldots\ldots(V)$$

A/C to S.S.A.; $d[I_2]/dt = 0$

$d[I_2]/dt = K_2[I_1][C] - K_3[I_2][R_3][C] = 0$

$K_2[I_1][C] = K_3[I_2][R_3][C]$ …….(VI)

From equation (V) and equation (VI)-

Rate = $K_2[I_1][C]$……..(VIII)

A/C to S.S.A.; $d[I_1]/dt = 0$

$d[I_1]/dt = K_1[R_1][R_2][C] - K_2[I_1][C]$

$K_1[R_1][R_2][C] = K_2[I_1][C]$ ……(IX)

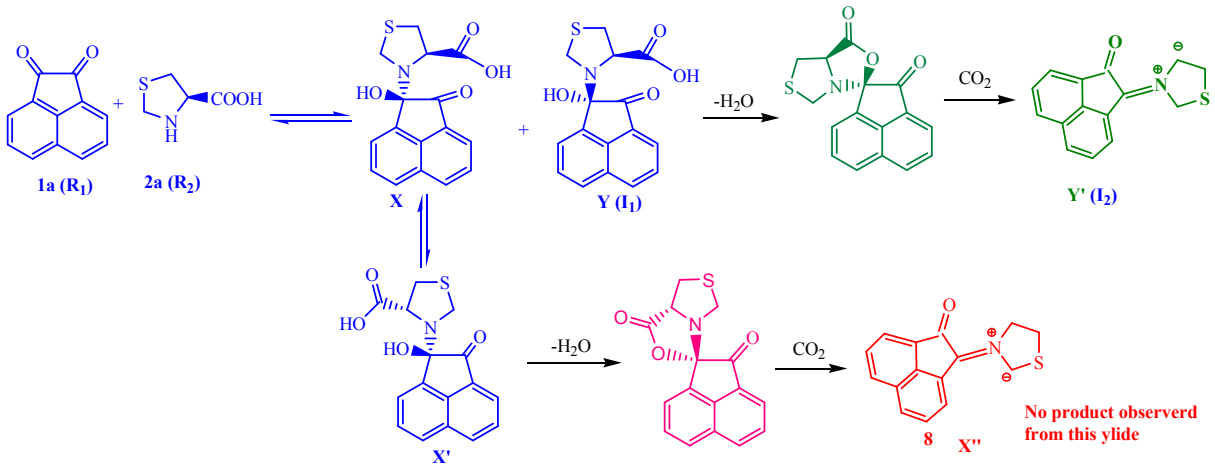
From equation (VIII) and equation (IX)-

Rate = $K_1[R_1][R_2][C]$

Only K_1 is present in rate law. So, first step (formation of intermediate 1) is rate determining step.

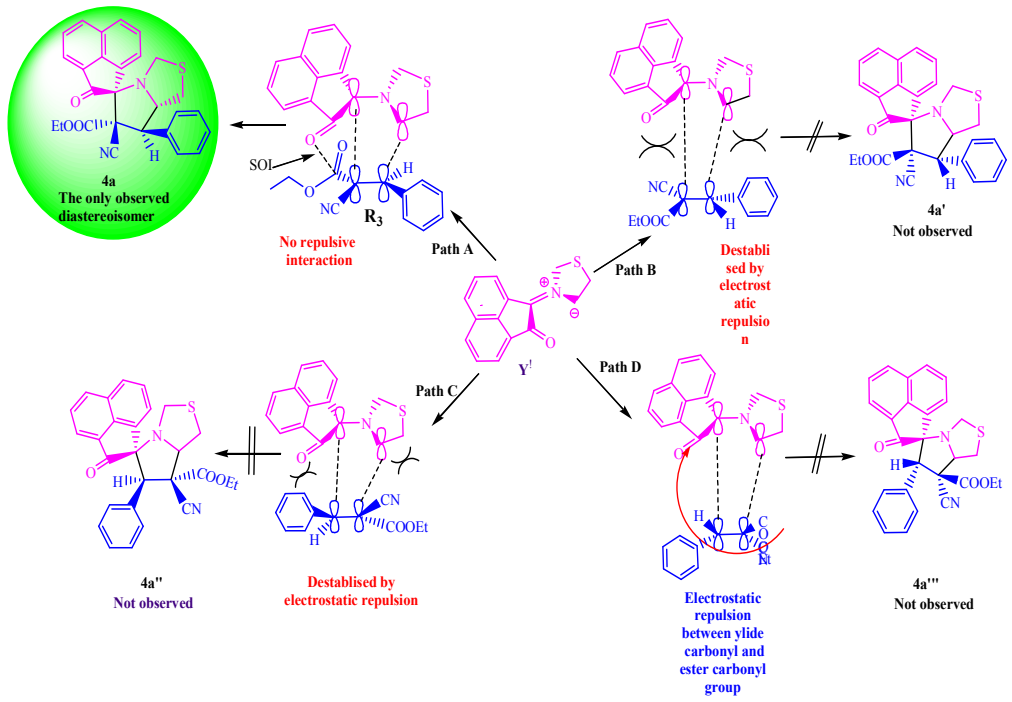
Plausible mechanism:

Although the detailed mechanism of the above reaction is not fully clarified, the formation of regioisomer **4** could be explained as follows: condensation of the acenaphthenequinone **1** (R_1) with 1,3-thiazole-4-carboxylic acid **2** (R_2) gives the intermediate 1 (I_1) which on decarboxylation gives the azomethine ylide (I_2). The azomethine ylide (I_2) subsequently undergoes 1,3-dipolar cycloaddition reaction with the dipolarophile **3** (R_3) to afford novel cycloadduct **4** as a single regioisomer. Since no stereoisomer of **4** originating from azomethine ylide X", it was implicit that Y' was formed utterly possibly due to some kind of attractive interaction[25] between carbonyl oxygen of acenaphthenequinone and carboxylic acid group of 1,3-thiazole-4-carboxylic acid (Scheme 4).



Scheme 4. Intermediacy of azomethine ylide

Due the presence of 4 stereocenters in the final product **4a**, there was the possibility of (2^4 = 16 stereoisomers) eight pairs of diastereoisomers. On the basis of the results obtained above, we noted here that the *E*-geometry of Knoevenagel adduct was conserved in the final product **4a**. 1,3-Dipolar cycloaddition reaction of dipolarophile and azomethine ylides proceed *via* concerted manner instead of step-wise biradical transition state[26]. Thus the reaction is stereospecific and the stereochemistry of 1,3-thiazole-4-carboxylic acid (**2**) and Knoevenagel adduct (**3**) would control the stereochemistry at1st, 2nd and 3rd stereocenteres (the stereocenters of **4** are marked as 1, 2, 3 and 4 in Scheme 5**).** The formation of only one distereomer and the stereochemical outcome of spiro-carbon (stereocenter no. 4) are explained on the basis of plausible transition state illustrated in Scheme 5. According to this, Path A is reasonably favoured by secondary orbital interaction (SOI) between carbonyl group (acenaphthenequinone ring) of azomethine ylide with the carbonyl group of dipolarophile (ester group)[27]. In Path B, the approach of ylide to dipolarophile appears to be destabilized by electrostatic repulsion between carbonyl group of acenaphthenequinone ring of ylide and carbonyl groups of ester group of dipolarophile as well as electrostatic repulsion between thiapyrrolidine reside of ylide and phenyl group of dipolarophile ruled out the possibility of formation **4a'**.



Scheme 5. Plausible transition state for the formation of 4a, 4a', 4a" and 4a '"

The observed regioselectivity can be explicated in the same way by considering HOMO-LUMO interactions of ylide and dipolarophile. As showed in Scheme 5, Path C lead to strong electrostatic repulsion between the carbonyl group of acenaphthenequinone ring of ylide and the aryl group of dipolarophile as well as electrostatic repulsion between ester group of dipolarophile and thiapyrrolidine reside of ylide. Additionally, strong electrostatic repulsion between the carbonyl group of acenaphthenequinone ring of ylide and the carbonyl group of ester part of dipolarophile (Path D) in the transition states agree well with the non-observation of regioisomers **4a″** and **4a‴**. In present study, reaction of azomethine ylide with alkene having electron withdrawing substituents occurs via $HOMO_{azomethineylide}$-$LUMO_{alkene}$. This interaction may be enhanced by the occurrence of electron withdrawing substituents on the dipolarophiles. Besides, activation of the alkenes results in a lowering of the energy of the LUMO and thus enhancement of rate as well as regioselectivity of reaction.

Finally, the regio- and stereochemical outcome of the cycloaddition was determined unequivocally by single crystal X-ray analysis of cycloadduct **4b** (Fig. 10, CCDC No-1039273). The ORTEP diagrams of **4b** clearly showed that the ester group and aryl group of dipolarophile is in trans orientation, which is obviously coming from the E-configuration of the starting

dipolarophiles. The two carbonyl groups of acenaphthenequinone ring and ester group of dipolarophile are in trans-relationship, which is explicable by the fact that the corresponding transition state (A) is logically favoured path due to secondary orbital interaction (SOI).

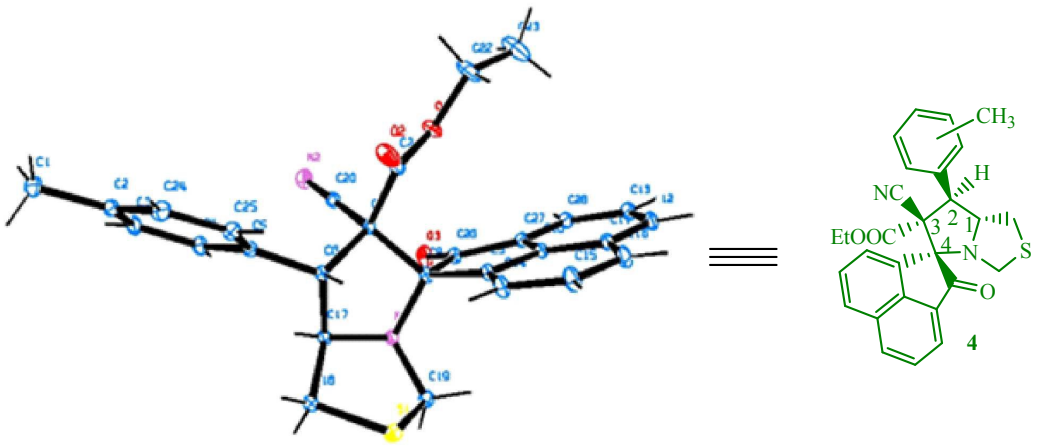


Fig. 10 ORTEP diagram of compound 4b. (CCDC No. 1039273)

3. EXPERIMENTAL SECTION

3.1. General

All the chemicals used were of research grade (purchased from Sigma Aldrich and Acros) and used without further purification. The melting points of all compounds were determined on a Toshniwal apparatus in capillary and uncorrected. IR spectra were recorded on a Shimadzu FT IR- 8400S spectrophotometer using KBr pellets. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ and DMSO-d_6 using TMS as an internal standard on a Bruker spectrophotometer at 400 and 75 MHz respectively. Chemical shifts are expressed in parts per million (ppm) using tetramethylsilane (TMS) as an internal standard. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet and m = multiplet. Mass spectrum of representative compound was recorded on Shimadzu GC-MS-QP-2010 spectrometer and Waters-Xevo G_2S Q-Tof spectrometer. X-ray intensity data were collected on Bruker Kappa Apex II diffractometer. The UV-Vis studies were performed using Ocean optics USB 2000 spectrophotometer.

3.2. General procedure for the synthesis of spiro[acenaphthylene-1,5′-pyrrolo[1,2-*c*]thiazole]

An equimolar mixture of acenaphthenequinone **1** (1 mmol), 1,3-thiazole-4-carboxylic acid **2** (1 mmol) and Knoevenagel adduct **3a-u** (1 mmol) and 10 mol% sodium chloride in 20 ml water were mixed and stirred at 80 °C for the appropriate time. The progress of the reaction was monitored by TLC (*with Merck plates pre-coated with silica gel 60 F_{254}; 0.25 mm thick*) by taking sample of the starting materials (**1, 2 and 3;** separately dissolved in ethyl acetate) as a reference on the left of the plate (spot no. 1, 2 and 3), a spot of the reaction mixture on the right (spot no. 5), and a co-spot of reactants and reaction mixture (spot no. 4). Then, TLC was run in benzene/ethyl acetate (8:2) (*eluent*). After running it, the spots on TLC plate were examined under UV lamp. The disappearance of spot of reactant **3** (Knoevenagel adduct: dipolarophile) on the TLC plate (*in spot no. 5th: spot of the reaction mixture*) and formation of a new spot (desired product) confirmed the completion of reaction. After completion of the reaction as indicated by TLC, the reaction mixture was cooled to room temperature, the water was decanted off, and the solid precipitates were crystallized (if required) to furnish pure spiro[acenaphthylene-1,5′-pyrrolo[1,2-*c*]thiazole] derivatives. All the synthesized compounds were well characterized by ^{1}H NMR, ^{13}C NMR, Mass and single crystal X-ray analysis.

4. Conclusions

In conclusion, we have highlight the role of NaCl for the regio- and stereoselective synthesis of spiro[acenaphthylene-1,2′-thiapyrrolizidine] derivatives through 1,3-dipolar cycloaddition reaction in aqueous medium. NaCl play a key role and enforced the hydrophobicity of water for the reaction and formed desired product in excellent yield. The imposed hydrophobic effect by NaCl+water system compared to other investigated systems is the causative/deciding factor for the reaction. The heterogeneous aqueous reaction systems, emphasize the magnitude of hydrophobic interactions on 1,3-dipolar cycloaddition reaction of azomethine ylides with olefins represents in aqueous medium for the first time. This strategy provides the formation of two C-C, one C-N bonds with four contiguous stereo centers including one spiro center in a one-pot reaction. The operational simplicity of this method, use of non-inflammable and nontoxic reaction medium, ease of product isolation/purification with no waste generation and the purity of the recovered products make it attractive to attain several principles of the green chemistry.

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References:

1. (a) M. Nyerges, L. Gajdics, A. Szollosy and L. Toke, *Synlett*, 1999, 111-113; (b) J. Dietz and S. F. Martin, *Tetrahedron Lett.*, 2011, **52**, 2048-2050; (c) J. Xue, Y. Zhang, X. -I. Wang, H. K. Fun and J. H. Xu, *Org. Lett.*, 2000, **2**, 2583–2586.
2. C. Marti and E. M. Carreira, *Eur. J. Org. Chem.*, 2003, 2209-2219.
3. (a) M. S. Chande, R. S. Verma, P. A. Barve and R. R. Khanwelkar, *Eur. J. Med. Chem.*, 2005, **40**, 1143-1148; (b) A. Dandia, M. Sati, K. Arya, R. Sharma and A. Loupy, *Chem. Pharm. Bull.*, 2003, **51**, 1137-1141; (c) Y. Ban, N. Taga and T. Oishi, *Chem. Pharm. Bull.*, 1976, **24**, 736-751; (d) Y. Ban, M. Seto and T. Oishi, *Chem. Pharm. Bull.*, 1975, **23**, 2605-2613; (e) T. Okita and M. Isobe, *Tetrahedron*, 1994, **50**, 11143-11152; (f) P. Rosenmond, M. Hosseini-Merescht and C. L. Bub, *Ann. Chem.*, 1994, **2**, 151-154; (g) M. A. Abou-Gharbia and P. H. Doukas, *Heterocycles*, 1979, **12**, 637–640; (h) M. J. Kornet and A. P. Thio, *J. Med. Chem.*, 1976, **19**, 892–898.
4. (a) L. Ming, G. Fu-Meng, W. Li-Rong and L. Zhao-Rui, *Eur. J. Org. Chem.*, 2011, **19**, 3482-3490; (b) D. Basavaiah, B. S. Reddy and S. S. Badsara, *Chem. Rev.*, 2010, **110**, 5447-5674; (c) R. R. Kumar, S. Perumal, P. Senthilkumar, P. Yogeeswari and D. Sriram, *J. Med. Chem.,* 2008, **51**, 5731-5735; (d) M. Ghandi, A. Taheri and A. Abbasi, *Tetrahedron*, 2010, **66**, 6744–6748; (e) R. Prasanna, S. Purushothaman, M. Suresh and R. Raghunathan, *Tetrahedron Lett.*, 2011, **52**, 792–797; (f) K. Kawashima, A. Kakehi and M. Noguchi, *Tetrahedron*, 2007, **63**, 1630-1643; (g) K. Ruck-Braun, T. H. E. Freysoldt and F. Wierschem, *Chem. Soc. Rev.*, 2005, **34**, 507-516.
5. (a) M. Boruah, D. Konwar and S. D. Sharma, *Tetrahedron Lett.*, 2007, **48**, 4535-4537; (b) R. R. Kumar, S. Perumal, P. Senthilkumar, P. Yogeeswari and D. Sriram, *Eur. J. Med. Chem.*, 2009, **44**, 3821-3829; (c) R. Rajesh and R. Raghunathan, *Tetrahedron Lett.*, 2010, **51**, 5845-5848; (d) J. Jayashankaran, R. Durga, R. S. Manian, R. Venkatesan and R. Raghunathan, *Tetrahedron*, 2005, **61**, 5595-5598; (e) S. Kathiravan, E. Ramesh and R. Raghunathan, *Tetrahedron Lett*., 2009, **50**, 2389-2391; (f) R. S. Kumar, S. M. Rajesh, S. Perumal, P. Yogeeswari and D. Sriramm, *Tetrahedron: Asymmetry*, 2010, **21**, 1315-1327.
6. (a) R. Jain, K. Sharma and D. Kumar, *Tetrahedron Lett.*, 2012, **53**, 1993–1997; (b) S. M. Rajesh, B. D. Bala and S. Perumal, *Tetrahedron Lett.*, 2012, **53**, 5367–5371; (c) A.

Hazra, Y. P. Bharitkar, A. Maity, S. Mondal and N. B. Mondal, *Tetrahedron Lett.*, 2013, **54**, 4339–4342.

7. (a) R. P. Swatloski, J. D. Holbrey and R. D. Rogers, *Green Chem.*, 2003, **5**, 361–363; (b) M. T. Garcia, N. Gathergood and P. J. Scammells, *Green*. *Chem*., 2005, **7**, 9–14; (c) M. Uerdingen, C. Treber, M. Balser, G. Schmitt and C. Werner, *Green Chem*., 2005, **7**, 321–325; (d) D. Zhao, Y. Liao and Z. Zhang, *Clean – Soil, Air, Water*, 2007, **35**, 42 – 48; (e) Y. Deng, I. Beadham, M. Ghavre, M. F. Costa Gomes, N. Gathergood, P. Husson, B. Légeret, B. Quilty, M. Sancelmea and P. Besse-Hoggan, *Green Chem*., 2015, **17**, 1479-1491.
8. (a) E. G. Feng, Y. Zhou, F. Zhao, X. J. Chen, L. Zhang, H. L. Jiang and H. Liu, *Green Chem*., 2012, **14**, 1888-1895; (b) Y. X. Su, Y. H. Deng, T. T. Ma, Y. Y. Li and L. P. Sun, *Green Chem*., 2012, **14**, 1979-1981; (c) C. -J. Li and L. Chen, *Chem*. *Soc*. *Rev*., 2006, **35**, 68-82; (d) V. Polshettiwar, B. Baruwati and R. S. Varma, *Chem. Commun.*, 2009, 1837-1839; (e) I. Hoffmann, B. Blumenröder, S. Onodineé Thumann, S. Dommer and J. Schatz, *Green Chem*., 2015, **DOI:** 10.1039/C5GC00794A; (f) P. Kleman, P. Barbaro and A. Pizzan, *Green Chem*., 2015, **DOI:** 10.1039/C5GC00485C.
9. (a) D. N. Kommi, D. Kumar, K. Seth and A. K. Chakraborti, *Org. Lett.,* 2013, **15**, 1158-1161; (b) S. V. Chankeshwara and A. K. Chakraborti, *Org. Lett.,* 2006, **8**, 3259-3262; (c) G. L. Khatik, R. Kumar and A. K. Chakraborti, *Org. Lett.,* 2006, **8**, 2433-2436; (d) I. Vilotijevic and T. F. Jamison, *Science,* 2007, **317**, 1189-1192; (e) N. Parikh, D. Kumar, S. R. Roy and A. K. Chakraborti, *Chem. Commun.,* 2011, 1797-1799; (f) N. E. Leadbeater, *Chem. Commun.,* 2005, 2881-2902.
10. (a) M. B. Gawande, V. D. B. Bonifa´cio, R. Luque, P. S. Brancoa and R. S. Varma, *Chem. Soc. Rev.*, 2013, **42**, 5522-5551; (b) V. Polshettiwar and R. S. Varma, *J. Org. Chem.*, 2007, **72**, 7420-7422; (c) C. -J. Li, *Chem. Rev.,* 2005, **105**, 3095-3166; (d) R. N. Butler and A. G. Coyne, *Chem. Rev.,* 2010, **110**, 6302-6337; (e) S. Minakata and M. Komatsu, *Chem. Rev*., 2009, 109, 711-234; (f) A. Chanda and V. V. Fokin, Chem. Rev. 2009, **109**, 725-748.
11. (a) R. Breslow, *Acc. Chem. Res.,* 1991, **24,** 317-324; (b) R. Breslow, K. Groves and M. U. Mayer, *Pure Appl. Chem.,* 1998, **70**, 1933-1938; (c) S. Otto and Jan B. F. N. Engberts,

Pure Appl. Chem., 2000, **72**, 1365–1372; (d) S. S. Pawar, U. Phalgune and A. Kumar, *J. Org. Chem.*, 1999, **64**, 7055-7060; (e) S. Tiwari and A. Kumar, *Chem. Commun.*, 2008, 4445–4447; (f) D. C. Rideout and R. Breslow, *J. Am. Chem. Soc*., 1980, **102**, 7816-7817.

12. (a) A. Dandia, R. Singh and S. Bhaskaran, *Ultrason. Sonochem*., 2011, **18**, 1113-1117**;** (b) A. Dandia, D. S. Bhati, A. K. Jain and G. N. Sharma, *Ultrason. Sonochem*., 2011, **18**, 1143-1147; (c) A. Dandia, V. Parewa and K. S. Rathore, *Catal. Commun.,* 2012, **28**, 90-94.
13. (a) A. Dandia, V. Parewa, A. K. Jain and K. S. Rathore, *Green Chem.,* 2011, **13**, 2135-2145; (b) A. Dandia, R. Singh, S. Bhaskaran and S. D. Samant, *Green Chem*., 2011, **13**, 1852-1859; (c) A. Dandia, V. Parewa, S. L. Gupta and K. S. Rathore, *J. Mol. Catal. A: Chem.*, 2013, **373**, 61-71;
14. (a) A. Dandia , S. L. Gupta , V. Parewa , A. Sharma, K. S. Rathore and A. Sharma, *Tetrahedron Lett.,* 2013, **54**, 5711-5717; (b) A. Dandia, R. Singh, J. Joshi, S. Maheshwari and P. Soni, *RSC Adv.*, 2013, **3**, 18992-19001; (c) A. Dandia, A. K. Laxkar and R. Singh, *Tetrahedron Lett*., 2012, **53**, 3012-3017.
15. A. Dandia, S. L. Gupta and V. Parewa, *RSC Adv.*, 2014, **4**, 6908–6915.
16. (a) R. Anness, A. L. Cooksy and M. Bergdahl, *J. Org. Chem.,* 2007,**72**, 5244-5259; (b) J. Dambacher, W. Zhao, A. El-Batta, R. Anness, C. Jiang and M. Bergdahl, *Tetrahedron Lett*., 2005, **46**, 4473-4477.
17. (a) A. Dandia, V. Parewa, S. L. Gupta, A. Sharma, K. S. Rathore, A. Sharma and A. Jain, *Catal. Comm.*, 2015, **61**, 88-91; (b) A. Dandia, V. Parewa, S. Maheshwari and K.S. Rathore, *J. Mol. Catal. A: Chem.,* 2014, **394**, 244-252.
18. (a) A. Dandia, A. K. Jain, A. K. Laxkar and D. S. Bhati, *Tetrahedron Lett*., 2013, **54**, 3180-3184; (b) A. Dandia, A. K. Jain and A. K. Laxkar, *RSC Adv*., 2013, **3**, 8422-8430; (c) A. Dandia, A. K. Jain, A. K. Laxkar and D. S. Bhati, *Tetrahedron*, 2013, **69**, 2062-2069; (d) A. Dandia, A. K. Jain and S. Sharma, *Tetrahedron Lett*., 2012, **53**, 5859-5863; (e) A. Dandia, A.K. Jain and D. S. Bhati, *Tetrahedron Lett*., 2011, **52**, 5333-5337.
19. (a) F. A. Long and W. F. McDevit, *Chem. Rev*., 1952, **51**, 119-169; (b) S. Endo, A. Pfennigsdorff and K. Goss, *Environ. Sci. Technol*., 2012, **46**, 1496-1503.
20. (a) W. –H. Xie, W. –Y. Shiu and Donald Mackay, *Marine Environ. Res*., 1997, **44**, 429-444; (b) A. Hasseine, A. -H. Meniai and M. Korichi, Desalination, 2009, **242**, 264-276.

21. (a) R. Breslow, U. Maitra and D. Rideout. *Tetrahedron Lett*. 1983, **24**, 1901-; (b) J. B. F. N. Engberts, *Pure &Appl. Chem.,* 1995, **67**, 823-828; (c) G. K. Van der Wel, J. W. Wijnen and J. B. F. N. Engberts. *J. Org. Chem*., 1996, **61**, 9001-; (d) R. Breslow and U. Maitra. *Tetrahedron Lett.* 1984, **25**, 1239-.

22. S. Endo, A. Pfennigsdorff and K. -U. Goss, *Environ*. *Sci*. *Technol.*, 2012, **46**, 1496-1503.

23. (a) W. Blokzijl, M. J. Blandamer and J. B. F. N. Engberts. *J. Am. Chem. Soc*., 1991, **113**, 4241-4246; (b) W. Blokzijl and J. B. F. N. Engberts, *J. Am. Chem. Soc*., 1992, **114**, 5440-5442.

24. (a) T. J. Mason, J. P. Lorimer and B. P. Mistry, *Tetrahedron*,1985, **41**, 5201-5204; (b) A. Tuulmets, *Ultrason. Sonochem*., 1997, **4**, 189-193.

25. R.A. Maurya, R. Nayak, C. N. Reddy, J. S. Kapure, J. B. Nanubolu, K. K. Singarapu, M. Ajithad and A. kamal, *RSC Adv*., 2014, **4**, 32303-32311.

26. (a) S. Lanka, S. Thennarasu and P. T. Perumal, *RSC Adv*., 2014, **4**, 2263-2266; (b) J. -A. Xiao, H. -G. Zhang, S. Liang, J. -W. Ren, H. Yang and X. - Q. Chen, *J. Org. Chem*., 2013, **78**, 11577-11583.

27. S. Haddad, S. Boudriga, F. Porzio, A. Soldera, M. Askri, M. Knorr, Y. Rousselin, M. M. Kubicki, C. Golz, and C. Strohmann, *J. Org. Chem.,* 2015, **80**, 9064-9075.

Imposed hydrophobic interactions by NaCl: Accountable attribute for the synthesis of spiro[acenaphthylene-1,5′-pyrrolo[1,2-*c*]thiazole] derivatives *via* 1,3-dipolar cycloaddition reaction in aqueous medium

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Graphical abstract