Tetrahedron 67 (2011) 7936–7945

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis of 2-amino-5-alkylidenethiazol-4-ones from ketones, rhodanine, and amines with the aid of re-usable heterogeneous silica-pyridine based catalyst

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ARTICLE INFO

Article history:
Received 8 April 2011
Received in revised form 11 August 2011
Accepted 12 August 2011
Available online 18 August 2011

Keywords:
2-Amino-5-alkylidenethiazol-4-ones
Ketones
Rhodanine
Amines
Dipolar catalyst
Silica based substituted pyridine

ABSTRACT

A new methodology has been developed towards the synthesis of novel 2-amino-5-alkylidenethiazol-4-ones from ketones, amines, and rhodanine. This is the first report of the use of ketones in contrast to aldehydes in all the earlier reported procedures. A new heterogeneous dipolar catalyst is designed and synthesized for this reaction. The unique properties of this catalyst facilitate the synthesis of such compounds. These 5-alkylidene rhodanine precursors display wide range of biological activities to possess antiviral, antimicrobial, cardiotonic and anti-inflammatory effects.

1. Introduction

The 2-amino-5-alkylidene-1,3-thiazol-4(5*H*)-ones and their 5-arylidene rhodanine precursors represent privileged scaffolds in drug discovery. A survey of recent papers dealing with the pharmacological properties of such compounds reveals that they display a wide range of activities. For example, compounds containing 2-amino-5-arylidene-1,3-thiazol-4(5*H*)-one moiety are reported to have antiviral,[1] antimicrobial,[2] cardiotonic,[3] and anti-inflammatory[4] effects. Among the anti-inflammatory agents, Darbufelone mesilate[5] (**1**) and PD-0167570 (**2**) [both in Fig. 1] are used as dual inhibitors[6] of cellular prostaglandin (PGF_{2a}) and leukotriene production (LTB_4). Additionally, Darbufelone is orally active in animal models of inflammation and arthritis[7] and is nonulcerogenic at very high doses.

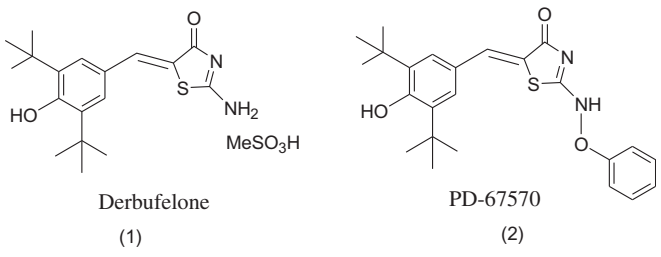

Fig. 1. Biologically active 2-amino-1,3-thiazol-4(5*H*)-one lead compounds.

Numerous synthetic routes[8–14] have been developed in order to obtain this heterocyclic core. However, all of them involve at least two subsequent steps with lengthy reaction times and laborious work-up. Thus, such methods are rather inconvenient. Pulici and Quartieri tried to overcome this by a traceless two-step solid-phase synthesis.[15] It involves reaction of rhodanine with bromo-Wang resin [4-(bromomethyl)phenoxymethyl polystyrene] in DMF under basic condition. This is immediately followed by a base catalyzed Knoevenagel condensation. Finally an exhaustive piperidine-mediated cleavage in DME–TFE (9:1) followed by silica-gel chromatography led to the recovery of the expected 2-amino-1-yl-thiazol-4-one. Therefore, it still suffers from a rather expensive solid support, lengthy reaction times and additional steps of loading of rhodanine on solid support and cleavage. Moreover, this protocol is not a very general one, working well for all aldehydes but not at all effective for ketones. Bourahla et al. reported an efficient microwave assisted one-pot tandem reaction.[16] They, employed aldimine instead of aldehyde to avoid the use of base in the Knoevenagel condensation step. However, it comprises a rather complicated sequence of reaction steps of generation of aldimines, addition of rhodanine followed by addition of secondary amines. In recent years, Anderluh et al. reported an acid catalyzed microwave

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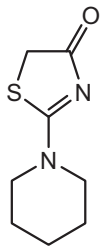
doi:10.1016/j.tet.2011.08.032

assisted three component one-pot synthesis of 2-amino-5-alkylidenethiazol-4-ones.[17] This condition worked well for all aldehydes but again not for ketones. In one of the papers,[18] Irvine et al. reported that despite employing conditions previously reported as suitable for condensing rhodanine with ketones,[19] they were unable to synthesize the compound from rhodanine and 3,4-dimethoxyacetophenone, the reasons being both steric and electronic. Till date, no general methodology is reported for ketones and only one or two isolated case of formation of 2-amino-5-alkylidenethiazol-4-ones from ketones is known. We therefore wish to disclose the development and implementation of a new methodology for the synthesis of 2-amino-5-alkylidenethiazol-4-ones with ketones. This is therefore the first report of describing the synthesis of 2-amino-5-alkylidenethiazol-4-ones from ketones, rhodanine and amines. It represents a very clean reaction condition, minimization of undesired product formation, high yield of the desired product and use of greener solvents.

Again the vast generality of the protocol makes it more acceptable than the previously reported methodologies, works well with aliphatic ketones; activated, neutral, hetero-aromatic, electron donating aromatic kerones; cyclic and acyclic secondary amines, as well as primary amines. Moreover employing our methodology we could smoothly synthesize the product from rhodanine, 3,4-dimethoxyacetophenone and amines, which was not possible with the earlier methodologies.[18]

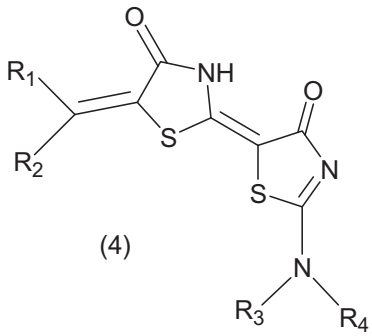
2. Results and discussion

We were particularly interested in the synthesis of 2-amino-5-alkylidenethiazol-4-ones from ketones, rhodanine and amines. It involves the displacement of rhodanine thiocarbonyl sulfur with the amine either directly or by activation via alkyl thioether, the resulting aminothiazolone being condensed with carbonyl via Knoevenagel condensation.[6b,15,20] Alternatively, rhodanine is first condensed with a carbonyl and the resulting alkylidene rhodanine is reacted with an amine.[14a–c,16,20a,b] The amine acts as the catalyst in the Knoevenagel condensation and as a nucleophile in the second step.[17] We, therefore, tried the reaction with equimolar quantity of rhodanine, 2-acetylthiophene and morpholine following the procedure for aldehyde reported by Anderluh et al. However, we isolated the compound (**3**) and unreacted ketone. Due to the low electrophilicity of the carbonyl carbon of ketones, the Knoevenagel condensation did not proceed at al. Therefore, use of a stronger base, prolonged reaction time and high temperature were essential for reaction with ketones.



(3)

However, long reaction times give rise to compounds (**4**) as side products.[21] The latter may arise from the nucleophilic displacement of an alkylidene thiazolone group by means of the anion generated on a second thiazolone moiety. Interestingly the amount of this type of side product depended also on the temperature and on the strength of the bases: in both cases, the greater the strength, the higher the yield.



(4)

The detrimental effect of excess amine to the yield is also reported.[17]Under high temperature and in presence of excess base, it is also expected for the ketones to undergo aldol type condensation or polymerization reaction. Therefore, use of equivalent amount of amine is an essential criterion for good yield and a clean reaction. In that case an additional base catalyst must be used for Knoevenagel condensation. This additional base catalyst must maximize the desired yield; minimize the side products, since it would minimize the reaction time and temperature. Therefore, it seems impossible for ketones to undergo such one-pot three-component condensation reaction affording 2-amino-5-alkylidenethiazol-4-ones in good yield and also in short reaction time. This is why no general methodology is still reported for ketones.

We were in search of a model catalyst that would simultaneously minimize the reaction temperature and time. It would increase the electrophilicity of the carbonyl carbon of the ketone by the coordination of oxygen lone pair with the Lewis acid site or Bronsted acid present in the catalyst. It would also have a basic site, and the basicity must be lower than amines to minimize waste production. Thus both the reaction time and temperature would be reduced.

The one-pot synthesis was optimized on a model reaction involving 2-acetylthiophene, rhodanine, and morpholine under a variety of conditions and the results are summarized in Table 1 (detailed optimization table is given in Supplementary data). The reaction was first tried with a slight excess (2 equiv) of morpholine under reflux in aqueous ethanol for 120 min. The yield (isolated) of the desired product was only 30%. As it is expected, the use of a Lewis acid, $FeCl_3$ as a co-catalyst reduced the reaction time to 60 min and yield also increased to 45%. Comparative yield was obtained with other Lewis acids like copper iodide, indium chloride, zinc chloride, and silver triflate. However, maximum yield of 50% was attained within 50 min when silica is used as a Lewis acid. This is due to the well documented fact that the silanol groups present on the silica coordinate with the carbonyl oxygen to increase its electrophilicity.[22,23] Decreasing the amount of morpholine to 1.2 mmol in presence of silica catalyst increased the yield to 63%. Interestingly, when we used equivalent amounts of morpholine and silica, we isolated the compound (**3**) and unreacted 2-acetylthiophene. Therefore, presence of a base is mandatory for the Knoevenagel condensation between rhodanine and ketones, particularly when equivalent quantity of amine is used. Therefore reagent quantity is optimized as 1 equiv of each of the amine, rhodanine, and ketone. In that case the use of a weak base catalyst and silica co-catalyst represents the most powerful methodology for preparation of 2-amino-5-alkylidenethiazol-4-ones with ketones. The yield decreased substantially when NaOH was used as a base catalyst. Decreasing the base strength increased the yield; however the reaction time was slightly extended. This is probably due to minimization of side product (**4**) with weaker base catalyst. Pyridine as a base gave maximum yield. Further decrease in base strength results in incomplete conversion. Some of the products obtained after silica-gel column chromatography was contaminated with the organic bases used as catalyst proven by ^{1}H NMR

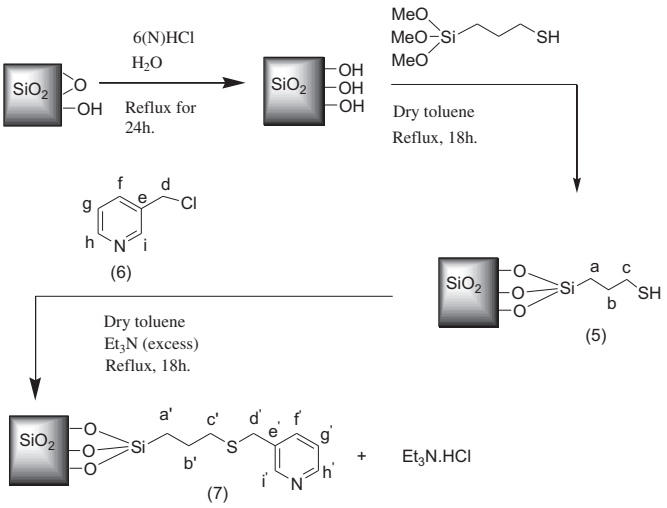
Table 1
Optimization of reaction conditions[a]

Entry	Amount of morpholine (mmol)	Base catalysts (mmol)	Lewis acid catalysts	Solvent (mL)	Time (min)	Isolated yields (%)
1	2.0	—	—	EtOH+H_2O (2+2)	120	15
2	2.0	—	Silica (40 mg)	EtOH+H_2O (2+2)	50	50
3	1.5	—	Silica (40 mg)	EtOH+H_2O (2+2)	55	61
4	1.2	—	Silica (40 mg)	EtOH+H_2O (2+2)	60	63
5	1.0	—	Silica (40 mg)	EtOH+H_2O (2+2)	120	0
6	1.0	NaOH (0.2)	Silica (40 mg)	EtOH+H_2O (2+2)	40	15
7	1.0	Ammonia (0.2)	Silica (40 mg)	EtOH+H_2O (2+2)	55	45
8	1.0	DABCO (0.2)	Silica (40 mg)	EtOH+H_2O (2+2)	56	50
9	1.0	Pyridine (0.2)	Silica (40 mg)	EtOH+H_2O (2+2)	70	65
10	1.0	Urea (0.2)	Silica (40 mg)	EtOH+H_2O (2+2)	240	10

[a] Reaction conditions: Rhodanine (1 mmol), 2-acetylthiophene (1 mmol), different amounts of morpholine, different base catalysts, under refluxing condition.

spectra. Particularly when *N*-methylpiperazine and dimethylamine are used in 2-amino-5-alkylidenethiazol-4-ones preparation, the compounds resulted became highly polar and were eluted from the column along with weak organic bases that were used. Therefore, additional crystallization became necessary.

Replacement of homogeneous organic base by a heterogeneous base of similar basic strength would overcome this problem. Therefore, we have designed and synthesized the following bi-functional silica based substituted pyridine catalyst (**7**) according to Scheme 1.



Scheme 1. Preparation of silica based substituted pyridine catalyst.

Thus we could avoid the harmful effect of pyridine and also combined the cooperative effect of silica and the organic base.

Here, we have chosen only 3-chloromethylpyridine and not the 2- or 4-substituted pyridine, because the displacement of chloride ion is assisted by the aromatic ring in 3-chloromethylpyridine (mechanism shown in Supplementary data). The canonical structures contain positive charge only on carbon atom. However, for 2- or 4-chloromethyl pyridine one of the canonical forms contains positive charge on nitrogen atom.

Using this catalyst we were able to synthesize a variety of 2-amino-5-alkylidenethiazol-4-ones from rhodanine (1 mmol), amines (1 mmol), and a variety of ketones (1 mmol) according to Scheme 2. Except for two cases the desired products (Table 2) were obtained in excellent yields.

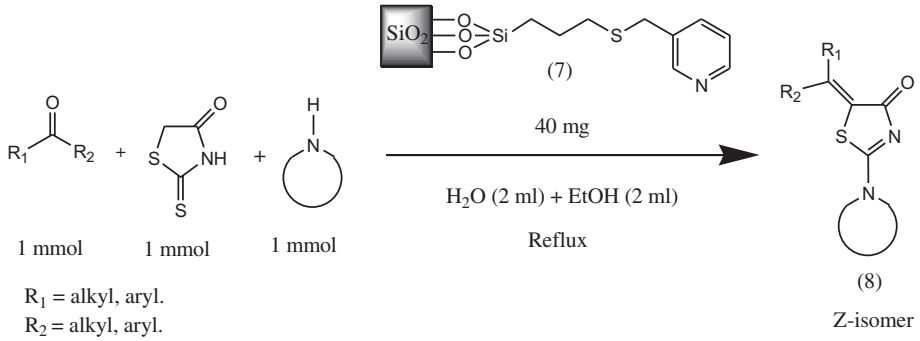
Here, 2-chloromethylpyridine moiety may provide straightforward possibilities for catalyst design, together with a simple immobilization procedure compared to other less- functionalized organocatalysts. Significant enhancement in product yield and a clean reaction condition was the outcome when the catalyst (**7**) was used. The products obtained after column chromatography were highly pure as proven from ^{1}H NMR spectra.

2.1. Product characterization

The products were characterized by IR, ^{1}H NMR, ^{13}NMR, HRMS, CHN analysis, and X-ray single crystal analysis. As only *Z*-isomers were produced with aldehydes in all previous reports,[15–17] for ketones also only the *Z*-isomers were produced as conformed from X-ray single crystal analysis of 2-dimethylamino-5-(1-thiophen-2-ylethylidene)-thiazol-4-one (**8n**) (Table 2, entry 14) (CCDC 812620).

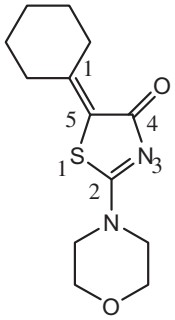
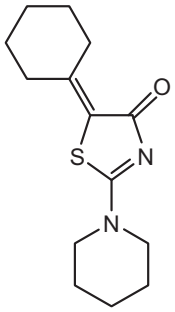
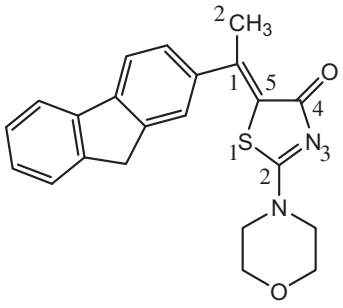
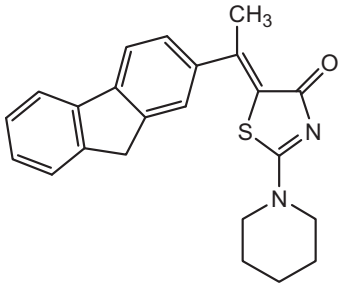
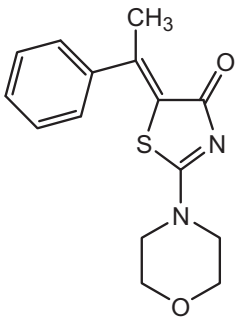
2.2. Mechanism

Here, condensation of rhodanine with amine preceded the Knoevenagel condensation as confirmed from the ^{1}H NMR spectra of the isolated product obtained by quenching the reaction of rhodanine, morpholine and 2-acetylfluorene after few minutes. This is in contrast to the aldehydes, where Knoevenagel condensation is the first step.[17] The quenching was done by simply



Scheme 2. Preparation of 2-amino-5-alkylidenethiazol-4-ones.

Table 2
Preparation of 2-amino-5-alkylidenethiazol-4-ones[a]

Entry	Compound numbering	Structure[b]	Time (min)	Melting Point (°C)	Isolated Yields (%)
1	**8a**		68	178–180	91
2	**8b**		66	172–174	91
3	**8c**		67	78–80	82
4	**8d**		65	—	93
5	**8e**		71	192–194	79

(*continued on next page*)

Table 2 (*continued*)

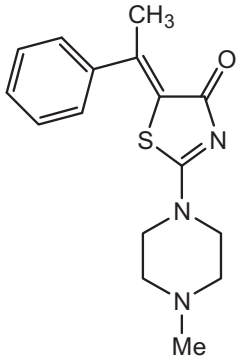
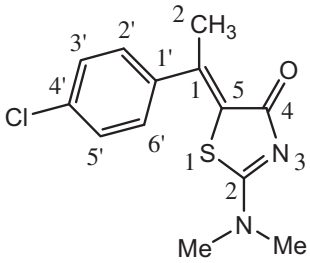
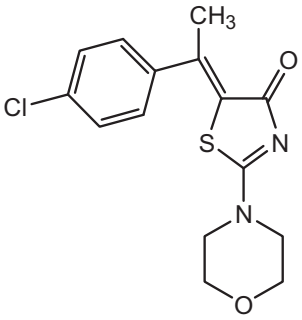
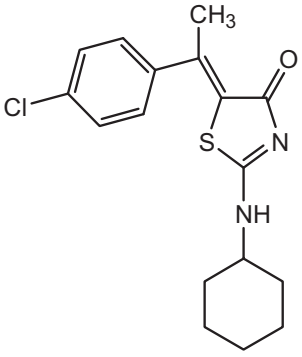
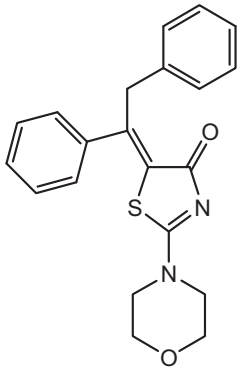
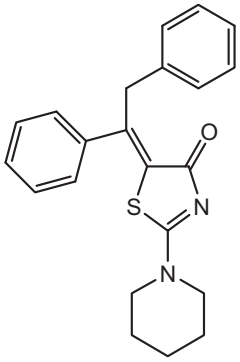
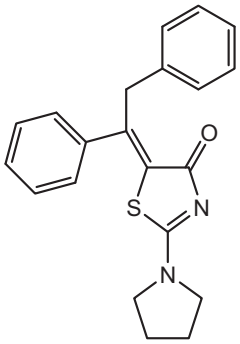
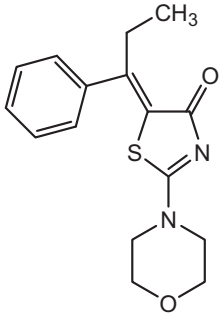
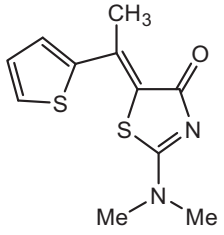
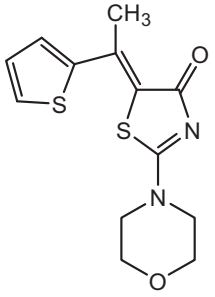
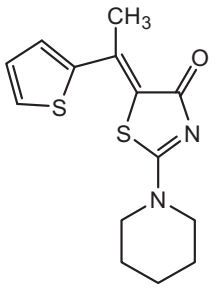
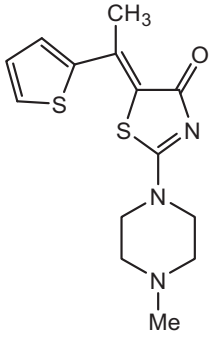
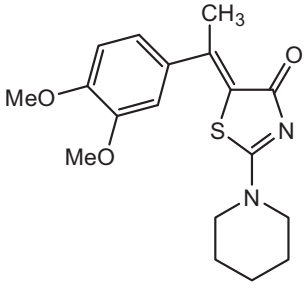
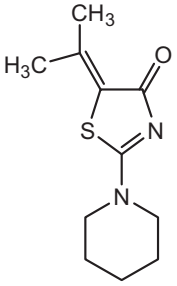
Entry	Compound numbering	Structure[b]	Time (min)	Melting Point (°C)	Isolated Yields (%)
6	**8f**		65	82–84	70
7	**8g**		71	—	62
8	**8h**		71	228–230	89
9	**8i**		78	224–226	86
10	**8j**		73	224–226	83

Table 2 (*continued*)

Entry	Compound numbering	Structure[b]	Time (min)	Melting Point (°C)	Isolated Yields (%)
11	**8k**		68	168–170	93
12	**8l**		67	190–192	73
13	**8m**		75	184–186	79
14	**8n**		72	158–160	68
15	**8o**		74	214–216	75

(*continued on next page*)

Table 2 (*continued*)

Entry	Compound numbering	Structure[b]	Time (min)	Melting Point (°C)	Isolated Yields (%)
16	**8p**		67	140–142	92
17	**8q**		65	82–84	65
18	**8r**		86	234–236	73
19	**8s**		50	172–174	82

[a] Reaction conditions: Rhodanine (1 mmol), ketones (1 mmol), amines (1 mmol), 40 mg silica based substituted pyridine catalyst (**7**), aqueous ethanol (1:1), reflux.
[b] The *Z*-diastereoselectivity is conformed from X-ray single crystal analysis of a compound (Table 2, entry 14).

removing the catalyst from the reaction mixture through filtration. Here, again lies the advantage of heterogeneous catalyst over homogeneous catalyst of similar basicity. The starting organic compounds remain in the homogeneous phase of aqueous ethanol. Since, the catalyst is heterogeneous, it is outside the homogeneous phase.[23] Water forms several hydrogen bonds between the nitrogen atom of catalyst (**7**) and the organic molecules, thereby acting as a bridge between the homogeneous and heterogeneous phases.[23] Here, water brings the active methylene groups to the lone pair of electrons of pyridine nitrogen of the catalyst through hydrogen-bonding (Fig. 2) and thereby favoring the ionization into carbanion donor.[23,24] The carbonyl oxygen coordinates with the silanol[22,23] groups on silica surface increasing the electrophilicity of the carbonyl carbon and thereby making it possible to carry out the reaction at a moderate temperature and in short time (Fig. 2). The formation of the *Z*-isomer may be explained by the plausible mechanism given below (Fig. 2). In the compound (**9**) generated by attack of rhodanine on ketone, the large group remains as far apart as possible as we have shown in Fig. 2. A subsequent cis-elimination explains the *Z*-diastereoselectivity in the final product. The cis-elimination is justified as the pyridine unit of the catalyst (**7**) approaches from the side in which the hydroxyl oxygen coordinates with the silanol group of the catalyst.

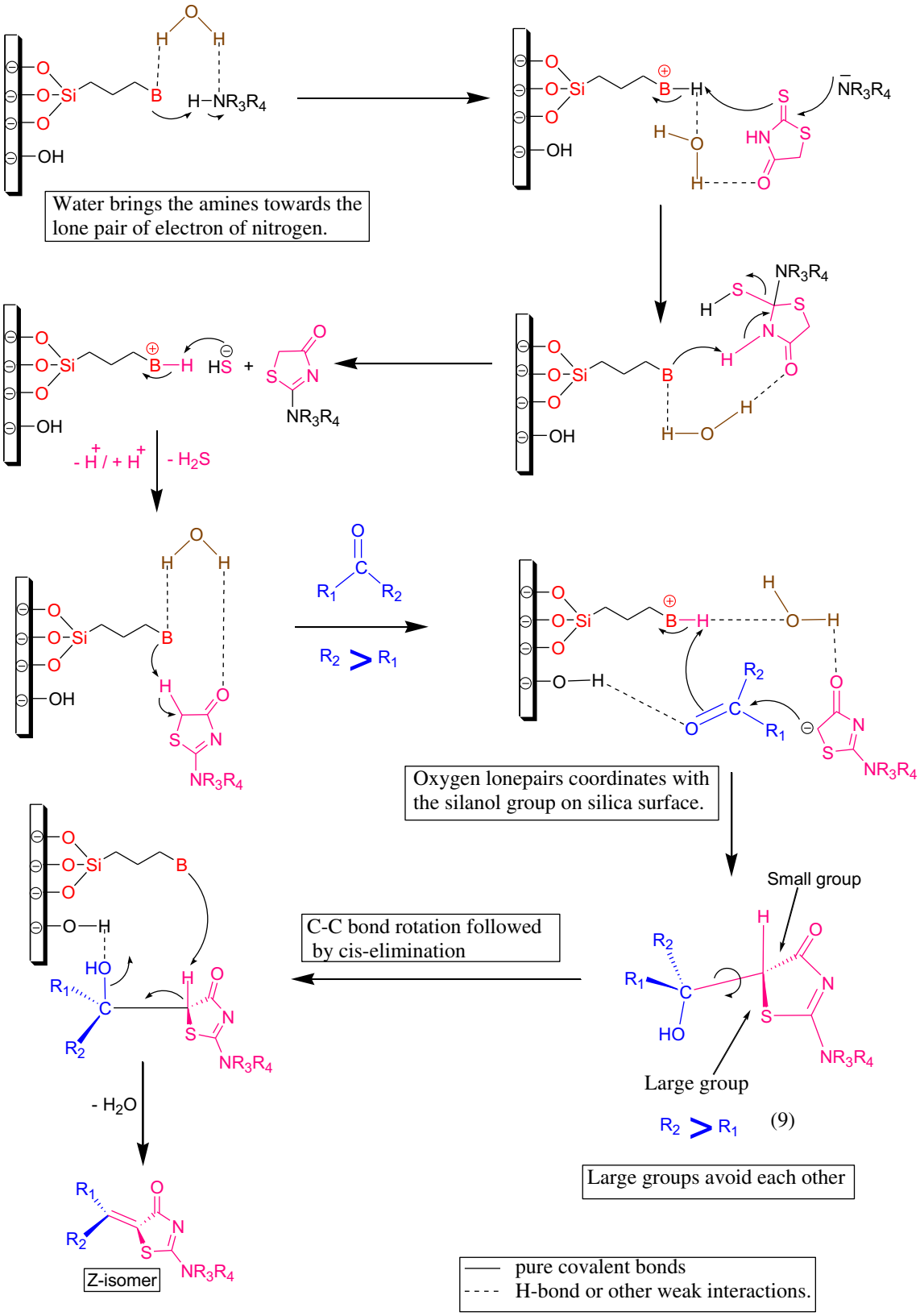


Fig. 2. Mechanism of preparation of 2-amino-5-alkylidenethiazol-4-ones.

2.3. Characterization of the catalyst

The catalyst (**7**) was characterized by solid state carbon 13 CP MAS NMR spectra, IR, elemental analysis, TGA studies, and pH experiment.

2.4. Carbon 13 CP MAS NMR spectra

The structure of mercaptopropylsilica[22,23,25–29] (**5**) has been characterized from our laboratory earlier by solid state carbon-13 CP MAS NMR spectrum. The solid state carbon-13 CP MAS NMR spectrum of (**5**) showed peaks at δ 26.9 corresponding to (b, c) and at δ 10.7 for (a). The prepared silica based substituted pyridine catalyst (**7**) was characterized by comparing the solid state carbon-13 CP MAS NMR spectrum of the prepared catalyst (**7**) with that of (**5**) and the normal solution phase carbon-13 NMR spectrum of 3-chloromethylpyridine (**6**). The normal solution phase carbon-13 NMR spectrum of 3-chloromethylpyridine showed peaks corresponding to δ 41.4(d), 127.4(g), 137.7(e), 141.6(f), 145.7, and 145.8 (for h and i). When the catalyst was prepared, the peak at δ 41.4 corresponding to (d) of 3-chloromethylpyridine vanished and appeared at δ 33.0 as (d′) along with (c′). This indicates that bond formation has taken place through carbon (d) and atom S. The remaining peaks for carbons showed slight deviations and appeared at δ 12.0 for (a′), 22.7 for (b′). The aromatic carbons appeared with little deviations at δ 130.4 (e′, g′), 146.8 and 148.4 (f′, h′, i′). This confirms the structure of the prepared silica based substituted pyridine catalyst (**7**).

2.5. IR spectra

When the samples are prepared using the well-known method of KBr pellet, infrared data are useful only to confirm the existence of the bonded species. Due to the low concentration of the organic part of modifier on the surface, the intensity of the new bands attesting the presence of organic groups is weak.[30] Hardly we observe any differences in the 2800–3000 cm^{-1} range, where ν(C–H) vibrations of the $-CH_2-$ groups are evidenced.[30] The strong and broad band in the range 3500–3400 cm^{-1} corresponds to the hydrogen bonded Si–OH groups and adsorbed water.[29,31] The signal at 3080 cm^{-1} is due to aromatic C–H stretching. The thio-propyl groups, which is attached to the silicon framework are identified by the methylene C–H stretching bands[29] at roughly 2940–2875 cm^{-1} and another broad at 1645 cm^{-1} is also due to O-H vibration of adsorbed water.[31] The weak signal between 1580 and 1450 is due to $=CH_2=$ bending and C=C and C=N ring stretching.[31] The band at 1222 cm^{-1} corresponds to the vibration of Si–C bond[29] and the sharp features around 1092 cm^{-1} indicated Si–O–Si stretching vibrations.[31] These results showed that the silica surface has been immobilized by covalent bonded organic molecules.

In addition to structural confirmation, quantitative determination of covalently anchored substituted pyridine group onto the surface of catalyst (**7**) was performed by elemental analysis, TGA analysis and ion-exchange pH analysis.

2.6. Elemental analysis

The elemental analysis of MPS (**5**) showed the carbon content to be 2.49%.[25] In the catalyst (**7**) the carbon and nitrogen content was found to be 7.00% and 0.91%, respectively, which ensured a total conversion of the mercapto group to the *S*-substituted pyridine unit. From this a loading of catalyst of 0.65 mmol/g was obtained.

2.7. TGA analysis

For silica-gel SiO_2 in the room temperature to 150 °C interval, a first loss of 2.4% is attributed to physisorbed water molecules released and a second loss of 2.9% from 150 to 600 °C is attributed to the condensation of silanol groups bonded to the surface and the remaining water molecules.[31] Different from silica gel, the silica based substituted piperidine catalyst (**7**) presents an additional 11.10% weight loss, mainly attributed to the organic arm. From this loss mass of organic arm a loading[23] of 0.67 mmol/g is obtained, which is very close to that obtained from elemental analysis.

2.8. pH analysis

To check the basic property of the prepared catalyst (**7**), the nitrogen atom of pyridine unit in the catalyst (**7**) was protonated with dilute HCl (details in the Supplementary data) and when 1 g of the protonated species was placed in 100 ml saturated NaCl solution, the pH of the resultant solution dropped to 3.50 since ion-exchange occurred between sodium ions and protons. From this ion-exchange pH analysis the same catalyst loading was obtained as that from elemental analysis.

2.9. Study on optimization of catalyst loading and choice of solvent

To study the effect of catalyst loading the reaction of rhodanine with 2-acetylthiophene and piperidine was chosen as model reaction. The results show clearly that silica based substituted pyridine (**7**) is an effective catalyst for this transformation and 40 mg of the catalyst was the optimum usage under this condition and the yields did not increase largely with higher amount of catalyst. It should be noted that, the yield was best[32] with EtOH–water [(2+2) mL]. The yield decreased substantially when the reaction was conducted in the presence of other solvents, such as CH_2Cl_2, ACN, and THF etc.

2.10. Recycling experiment

The possibility of recycling the catalyst was examined using the reaction of 4′-chloroacetophenone with rhodanine and morpholine under optimized conditions. The recycled catalyst could be used at least eight times without any further treatment. Detailed characterization of the catalyst after first run showed that it was unaffected under the condition of the reaction. Elemental analysis of the recovered catalyst after first run showed carbon and nitrogen content to be 6.8% and 0.88%, respectively, and a catalyst site loading of 0.63 mmol/g was obtained which was almost same with the original catalyst (0.65 mmol/g). The TGA diagram of the recovered catalyst showed same pattern with the original catalyst. From TGA also almost same catalyst loading was obtained as that of original catalyst. In IR also no additional peak appeared and only the original peaks retained. This may be due to the fact that since the amino group of the catalyst is tertiary in nature, it does not interact with the starting materials. A negligible loss in the catalytic activity of silica based substituted pyridine catalyst was observed (Table 3). The slightly extended time for the recycles is probably due to loss of some amount of catalyst in the time of filtration.

3. Conclusion

In conclusion, we have developed a rather novel protocol using a new silica-based heterogeneous catalyst for the one-pot three-component synthesis of 2-amino-5-alkylidenethiazol-4-ones from rhodanine, amines, and ketones in contrast to the aldehydes in all

Table 3
Recycling of silica based substituted pyridine catalyst (**7**) for the reaction of 4′-chloroacetophenone with rhodanine and morpholine[a]

Cycles[b]	Time (min)	Yield[c] (%)
1	71	89
2	71	84
3	75	84
4	77	81
5	76	83
6	83	79
7	90	81
8	95	75

[a] Reaction conditions: Rhodanine (1 mmol), 4′-chloroacetophenone (1 mmol), morpholine (1 mmol), 40 mg silica based substituted pyridine catalyst (**7**), aqueous ethanol (1:1), reflux.
[b] Rection was carried with recovered catalyst.
[c] Isolated yield.

the earlier reported methods. This is the first report of a methodology describing the synthesis of 2-amino-5-alkylidenethiazol-4-ones from ketones. It represents a powerfully green technology procedure for the use of environmental friendly solvent and prevention of unwanted waste production. Shorter reaction times and one-pot strategy make it convenient for parallel synthesis.

Acknowledgements

One of the authors (S.R.) thanks the Council of Scientific and Industrial Research, New Delhi for his fellowship (JRF). We thank the CAS Instrumentation Facility, Department of Chemistry, University of Calcutta for spectral data. We also acknowledge grant received from UGC funded Major project, F. No. 37-398/2009 (S.R.) dated 11-01-2010. Moreover, NMR Research Centre, IISc, Bangalore-560012 is gratefully acknowledged for the solid state carbon-13 CP MAS NMR spectrum.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.08.032.

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