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# Synthesis of molecular scaffolds assimilating both indolinone and thiazolidinone moieties under environmentally benevolent conditions

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ABSTRACT

A chromatography free synthesis of 2-amino-5-isatinylidenethiazol-4-ones from rhodanine, isatin, and amine under environmentally benevolent conditions is reported for the first time. The molecular scaffolds assimilating both indolinone and thiazolidinone moieties are reported to have great biological significance.



Post-translational modification of proteins by poly ADP-ribosylation regulates many cellular pathways that are critical for genome stability including DNA damage repair, chromatin structure, mitosis, transcription, RNA metabolism, and telomere function.[1] Poly ADP-ribose (PAR) is composed of repeating ADP ribose units linked via a unique glycosidic ribose–ribose bond.[1a,b] The poly(ADP-ribose) polymerase (PARP) family of enzymes, most notably PARP-1, use β-NAD+ in the synthesis of poly(ADP-ribose).[1d,e] The presence of PAR is transient due to the high specific activity of poly(-ADP-ribose) glycohydrolase (PARG), the main enzyme involved in the degradation of PAR.[1d] PARG catalyzes the hydrolysis of the ribosyl-ribose bond of PAR chains; its deficiency leads to cell death.[1a,2] Thus, inhibition of PARG activity may be a viable strategy for cancer treatment, selective small molecule inhibitors of PARG would greatly aid in the interrogation of this interesting biological target.[1d] Unfortunately, the lack of potent, specific, and easily synthesized small molecule inhibitors of PARG has limited the study of PARG's function both in vitro and in vivo. In recent years an extensive study revealed that from an in-house collection of 224 rhodanine containing small molecules, 72 compounds containing the **isatinylidenerhodanine** moiety were selected and screened for their ability to inhibit PARG in vitro at 10 μM. Many of them showed really promising PARG inhibitor activity (Fig. 1).[1d]

Isatinylidenerhodanine-containing biologically active molecules have also been evaluated to show activity against grampositive and gram-negative bacterial infections.[3] Substituted isatinylidenerhodanines can also be used as potential therapeutics for the treatment of neurodegenerative diseases,[4] diabetes,[5] sleep, and mood disorders.[6] Moreover, they have been used in developing molecular probes to evaluate the activities of biological targets.[7] Therefore, the quest of the organic chemists has been devoted to access functionalized isatinylidenerhodanines in satisfactory yields under mild conditions.

The 'greening' of global chemical processes has become a major issue in the chemical industry and in biology both in terms of selection of reactions and for the study of solvent and catalyst effects.[8] The development of new strategies for recycling catalysts, which minimizes the consumption of auxiliary substances, energy, and time required in achieving separations can result in significant economic and environmental benefits.[8a,9,10] Heterogenization of catalysts through synthesizing inorganic–organic hybrid materials has been an interesting approach during the past years. This strategy enabled the research groups to overcome the limitations involved in the separation and recycling of the homogeneous catalysts. Immobilization of the homogeneous catalyst onto the solid material through chemical bonding is one of the most powerful strategies to overcome the negative aspects of catalyst leaching. To achieve this goal, it is necessary to use a linker with chemical bonding between catalyst and support.[11] The use of a combination of inorganic materials and organic functional groups often results in synergetic effects that lead to increased physical stability and enhanced chemical functionality.[12] In this respect it should be mentioned that silica has some additional advantages over other heterogeneous solid supports, the most important of which is the relatively easy covalent modification of the surface of silica with

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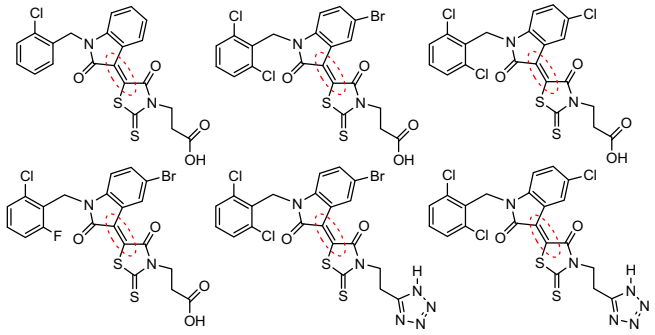
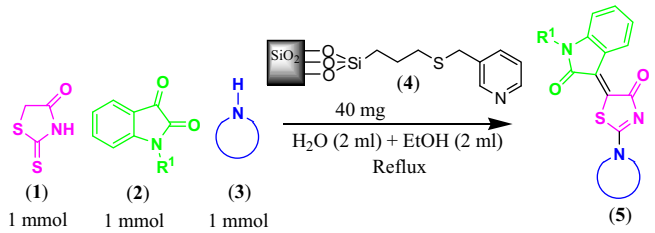


**Figure 1.** Some **isatinylidenerhodanine** containing drug molecules.



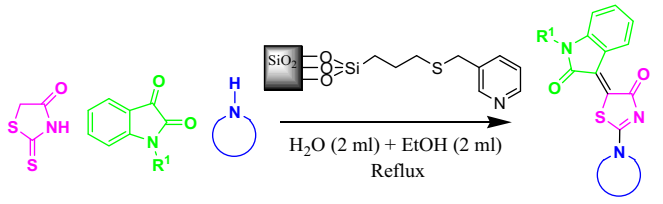

**Scheme 1.** Synthesis of 2-amino-5-isatinylidenethiazol-4-ones.

organic, inorganic, or organometallic moieties due to the presence of surface silanol groups. Additionally, silica possesses excellent physicochemical properties and is inert under reaction and during processing.[13]

Inspired by these foregoing discussions and given our interest and experience in the area of heterogeneous catalysis in organic synthesis,[13–20] we herein report the preparation of a new type of 2-amino-5-isatinylidenethiazol-4-ones (**5**) with the aid of a re-usable heterogeneous silica–pyridine based catalyst[17,18] (**4**) (Scheme 1) starting from rhodanine (**1**), isatin (**2**), and amine (**3**).

A survey of the literature revealed that *albeit* the Knoevenagel condensation between isatin and rhodanine is seldom reported,[1d,3e,21] to the best of our knowledge no attempt has been

**Table 1**
Optimization of reaction conditions[a]




| Entry | Solvent (4 ml) | Temp | Time (h) | Yield[b] (%) |
|---|---|---|---|---|
| 1 | DCM | 25–30 | 48 | 15 |
| 2 | DCE | 80–85 | 24 | 35 |
| 3 | Toluene | 90–100 | 16 | 40 |
| 4 | Acetone | 50–55 | 24 | 38 |
| 5 | THF | 60–65 | 24 | 42 |
| 6 | MeOH | 60–65 | 16 | 45 |
| 7 | EtOH | 75–80 | 16 | 85 |
| 8 | $H_2O$ | 90–100 | 20 | 61 |
| 9 | EtOH–$H_2O$ (2+2 ml) | 80–90 | 12 | 88 |
| 10 | EtOH–$H_2O$ (2+2 ml) | 55–60 | 16 | 50 |

[a] Reaction condition: Rhodanine (1 mmol), isatin (1 mmol), piperidine (1 mmol), 40 mg catalyst (**4**), different solvents, different temperature, different time, and reflux.
[b] Isolated yields.

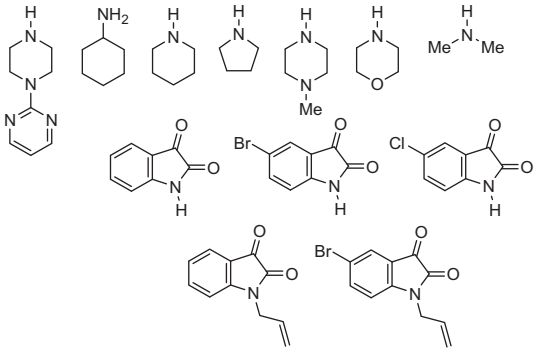


**Figure 2.** Substrate scope for amine and isatin.

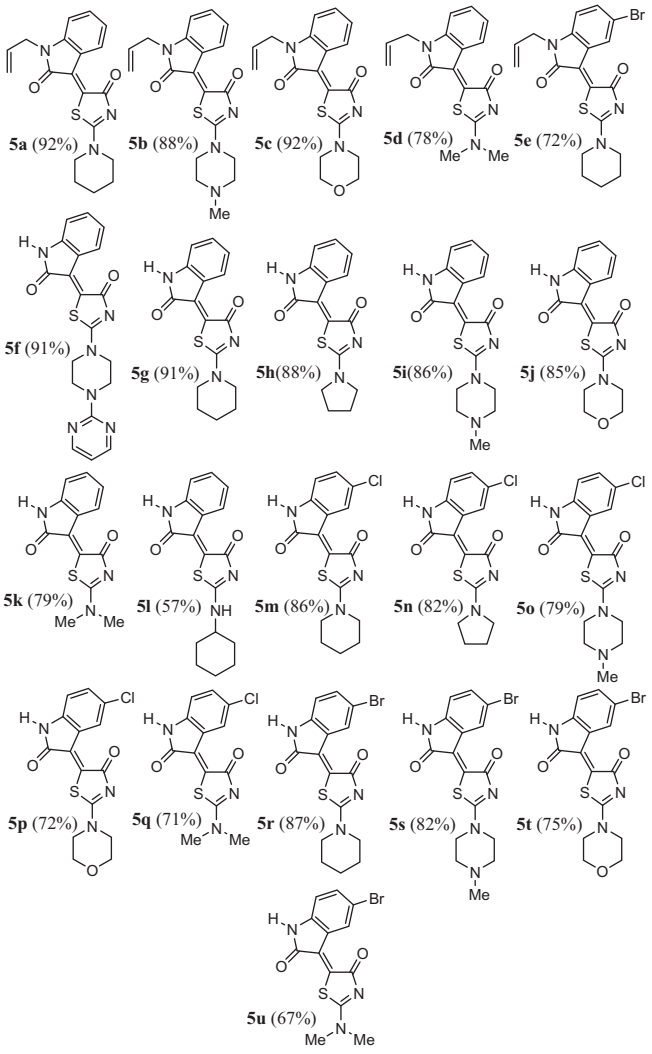
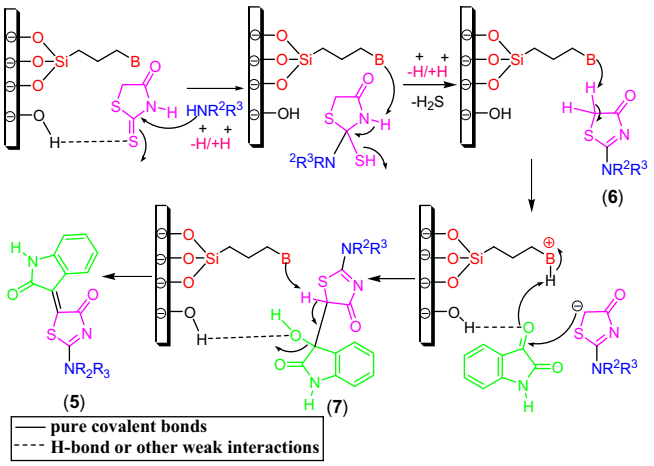



**Figure 3.** Library of 2-amino-5-isatinylidenethiazol-4-ones synthesized.

made so far to investigate the 3-component reaction between rhodanine, amine, and isatin to fabricate a new kind of thiazolidinone derivative for further bioassay.

In order to ascertain the feasibility of this transformation, the reaction between rhodanine, piperidine, and isatin was selected as a model substrate and studied under a variety of conditions. Several common solvents, viz. DCE, DCM, toluene, THF, EtOH, MeOH, and water were tested (Table 1). Though the yields of the reaction increased in polar-protic solvent than aprotic and non




**Scheme 2.** Plausible mechanism for 2-amino-5-isatinylidenethiazol-4-ones formation.

polar solvents, the reaction was not satisfactory in water (Table 1, entry 8), possibly due to less homogeneity of the reaction mixture. Therefore aqueous-ethanol (1:1 v/v) came out as a best choice of solvent. Similarly, temperature appears to play a significant role because there was only 50% conversion after stirring the reaction mixture at 55–60 °C for 8 h (Table 1, entry 10) in aqueous ethanol instead of 91% yield at 80–90 °C (Table 1, entry 9).

With the optimized conditions in hand, to delineate this approach, the scope and generality of this protocol was next examined by employing five different isatins and seven different amines (Fig. 2). An assembly of 21 compounds was synthesized using this protocol (Fig. 3).

Encouraged by the success of the above reaction, we became interested in the mechanism (Scheme 2). For this purpose, we investigated the reaction of rhodanine, *N*-allyl isatin, and morpholine. The process commenced with the reaction between rhodanine and amine to afford compound (**6**) as evidenced from the crude reaction mixture isolated after 1 h. The compounds detected in the $^1$H NMR spectra of the crude reaction mixture isolated after 1 h were the intermediate (**6**) and the unconsumed *N*-allyl isatin with only 7% of the target molecule (**5c**) (Figure given in Supplementary data). Intermediate (**6**) was isolated from the crude reaction mixture by chromatographic separation and its structure was determined by NMR spectroscopy. Again the target compound (**5c**) was also obtained when the intermediate (**6**) was refluxed in aqueous-ethanol with *N*-allyl isatin in presence of the catalyst (**4**) for 10 h. Thus the intermediacy of **6** in this transformation is clearly established. These facts altogether support the proposed mechanism. We have reported[15] in one of our recent papers that the attack of amine (**3**) on C=S of rhodanine (**1**) is an acid catalyzed reaction and in the present work silica performs efficiently as an acid catalyst to afford the in situ intermediate (**6**). The intermediate then suffers a concomitant Knoevenagel type condensation with isatin to give the target compound (**5**). This step is catalyzed by the covalently anchored pyridine moiety in the catalyst.[17,18] Compound **6** was solely formed only with silica without the formation of any desired compound **5**. Therefore a base catalyst is indispensable for the Knoevenagel condensation between isatin and the compound **6**. The amines employed here cannot act as a base since they all are consumed by compound **6** when they are used in equivalent quantity. Although the reaction was successful with 1.1 equiv of amine with silica as an acid catalyst, it produced very low yield. Literature survey divulges that the detrimental effect of excess amine to the yield is presumably due to the formation of the unwanted product (**8**) whose quantity increases with the strength of the base (Fig. 4).[17,18,22] The latter may arise from the nucleophilic displacement of an isatinylidenethiazolone group by means of the anion generated on a second thiazolone moiety. Again green chemistry aims to eliminate pollution by preventing it from happening in the first place and by using resources for chemical products that are renewable.[8a,10] Therefore the excess amine (**3**) must be replaced with a heterogeneous reusable catalyst and if its basicity is lower than the amine (**3**) used then it is a double achievement since green chemistry not only prioritizes the use of reusable catalysts but also the product yield. Thus the best yield, cleanest reaction, and most facile work-up were achieved employing 1.0 equiv of each of rhodanine (**1**), isatin (**2**), and amine (**3**) employing 40 mg of silica based substituted pyridine (**4**) as the right choice of catalyst and was demonstrated to be the key to obtain good to excellent yields of (**5**).

On the basis of the foregoing discussion a plausible reaction scenario for this one pot three-component reaction is outlined in Scheme 2. From this we can conclude that both acid and base functionalities are inevitable for this transformation. In this present instance the silica-pyridine based catalyst (**4**) performs efficiently as a heterogeneous ditopic catalyst containing both acid and base functionalities. The key findings of high significance of the catalyst described in this work are threefold. Firstly the attack of the secondary amine (**3**) on C=S of rhodanine (**1**) is catalyzed by acidic silica. Secondly the silanol groups present on the surface of silica coordinate with the oxygen atom of the isatin carbonyl which in turn increases its electrophicity[15–18] and the attack of rhodanine becomes easier affording the compound (**7**). Subsequent water elimination from (**7**) is also greatly assisted by the catalyst to give the target compound (**5**).

The third high significance is that the leaching of the active site is greatly avoided as the pyridine moiety is covalently attached with the silica surface through a silanol group.

Good to excellent conversion was also achieved with different homogeneous catalyst like NaOAc/AcOH, $NH_4OAc$/AcOH, piperidinium benzoate etc. However they required repeated work-up, neutralization of acids and bases, and extensive chromatographic purification. Ultimately the isolated yields were very low. The reactions with different spinel metal oxide nano particles containing both acidic and basic sites like $ZnTiO_3$ and $ZnFe_2O_4$ afforded comparatively low yield.

The structures of the compounds (**5**) were determined by IR, $^1$H, $^{13}$C NMR, CHN, and X-ray single crystal analysis. The scanned copies of $^1$H and $^{13}$C NMR spectra of all the compounds are given in Supplementary data. It is worthy to declare that the 'Z' geometry of the olefinic bond was explicitly assigned from X-ray single crystal analysis of (**5d**) (**CCDC 939929**) (Fig. 5). To the best of our knowledge structural determination of isatinylidenerhodanine compounds by X-ray single crystal analysis has not been reported.

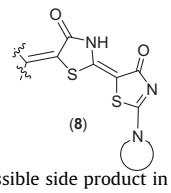


**Figure 4.** Possible side product in this reaction.

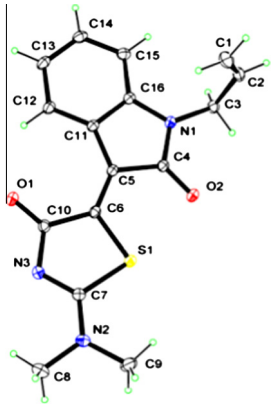



**Figure 5.** ORTEP diagram of **5d** (**CCDC 939929**).

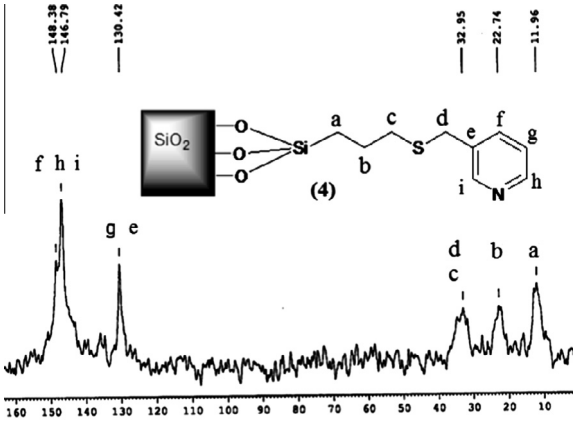



**Figure 6.** $^{13}$C CP MAS NMR spectra of catalyst (**4**).

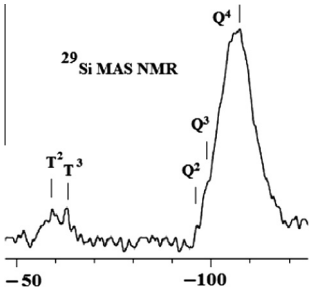



**Figure 7.** $^{29}$Si MAS NMR spectra of catalyst (**4**).

The catalyst was prepared according to the procedure we have reported previously.[16–18] In the $^{13}$C CP MAS NMR spectra (Fig. 6) the catalyst showed peaks at $\delta$ 12.0 for (a), 22.7 for (b), 33.0 for (c and d), 130.4 for (e and g), 146.8, and 148.4 for (f, h, and i). This confirmed the structure of the prepared silica based substituted pyridine catalyst (**4**).

The $^{29}$Si MAS NMR spectral pattern for silica supported pyridine catalyst is shown in (Fig. 7). Three up resonance peaks assigned to tetrahedral $Q^2$ (−96 ppm), $Q^3$ (−101 ppm) and $Q^4$ (−111 ppm) silica species,[23] respectively, where $Q^n = Si(OSi)_n(OH)_{4-n}$, $n = 2–4$. Again the high $Q^4$ percentage indicated highly condensed network.[24] Such a high $Q^4$ concentration is of paramount importance for the catalytic activity of the silica based catalyst, since the reduction of surface silanols introduces high hydrophobicity (and thus more affinity toward organic substrates).[24] The down field

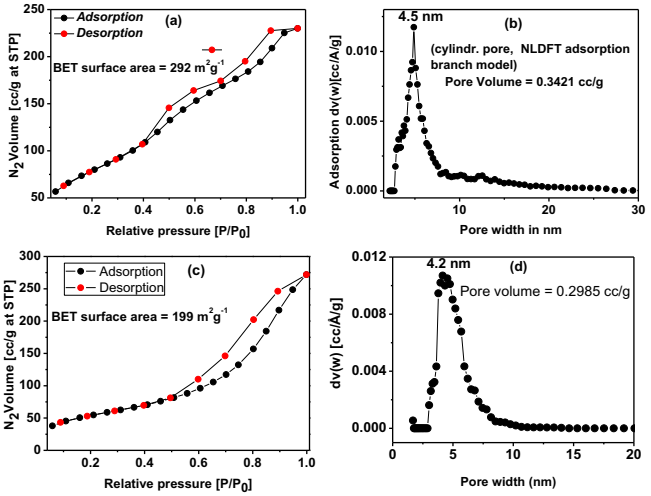



**Figure 8.** (a) $N_2$ adsorption isotherm and (b) PSD of silica; (c) $N_2$ adsorption isotherm, and (d) PSD of catalyst (**4**).

peaks at −58 ppm assigned to Si–OH of $RSi(OSi)_2(OH)$ group ($T^2$) and −66 ppm assigned to $R–Si(OSi)_3$ group ($T^3$), which provides direct evidence that the hybrid catalyst (**4**) consists of a highly condensed siloxane network with an organic group covalently bonded to the silica gel as a part of the silica wall structure.[23]

Nitrogen adsorption isotherms of different samples were recorded. The Brunauer–Emmett–Teller surface area of the silica obtained by using $N_2$ adsorption–desorption isotherm was found out to be 292 $m^2\ g^{-1}$ and pore volume was 0.3421 cc/g (Fig. 8, panel a and b). We can find that the surface area (199 $m^2\ g^{-1}$) and pore volume (0.2985 cc/g) of the catalyst (**4**) decreases when compared to pure silica (panel c and d). It is expected for organic-functionalized silica due to the occupation of large organic groups in the small pores, that is, restricted access to the pores caused by organic functional group. Therefore, the organic functionality is grafted compactly and securely inside the pores while not fully occupying the total available space, therefore still leaving room for $N_2$ adsorption and molecular transport. NLDFT pore size distribution (PSD) results of the catalyst showed a wide distribution of pores with peak pore dimension of ca. 4.2 nm.

Reactions were carried out using different amounts of the catalyst and the optimum amount has been determined. We can see that yield increases only marginally with increasing amount of catalyst from 40 to 70 mg. Since we wanted to use minimum quantity of catalyst, 40 mg was determined as the optimum amount. Determination of this optimum amount to achieve maximum yield was very essential to establish the efficacy and broaden the applicabil-

**Table 2**
Optimization of the amount of catalyst[a]

| Entry | Amount of catalyst (mg) | Conversion[b] (%) |
|---|---|---|
| 1 | 0 | 0 |
| 2 | 5 | 14 |
| 3 | 10 | 27 |
| 4 | 20 | 43 |
| 5 | 30 | 65 |
| 6 | 40 | 88 |
| 7 | 45 | 89 |
| 8 | 50 | 89 |
| 9 | 60 | 89 |
| 10 | 70 | 90 |

[a] Reaction condition: Rhodanine(1 mmol), *N*-allyl isatin (1 mmol), *N*-methyl piperazine (1 mmol), different amounts of silica based pyridine catalyst, and aqueous ethanol (2+2 ml), 80–90 °C reflux for 12 h.
[b] Percentage was calculated from crude $^1$H NMR spectra (300 MHz).

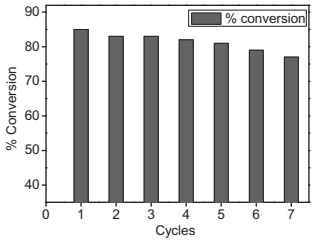



**Figure 9.** Recycling of catalyst (**4**) for the reaction forming **5j**.

ity of the proposed process. For this purpose the reaction forming **5b** was chosen as a test reaction (see Table 2).

In the presence of the catalyst (preheated at 100 °C for 4 h) the reaction between isatin, rhodanine, and morpholine occurred with 85% yield of **5j**. The same reaction in the presence of the catalyst after having it exposed to ambient atmosphere for 5 days produced similar observation. Obviously, there was no deteriorating effect of heat, aerial oxygen, or moisture toward the activity of the catalyst. The recycled catalyst could be used at least seven times with almost the same efficiency as that of first run without any further treatment (Fig. 9). Detailed characterization of the catalyst after the 5th run showed that it was unaffected under the conditions of the reaction.

Therefore, the aim of this protocol[25] is to highlight the synergistic effects of the combined use of multi-component reactions in an environmentally benevolent solvent and the application of solid base catalyst supported on silica with inherent properties like reusability and robustness for the development of new eco-compatible strategy for heterocyclic synthesis. The spectral and analytical data[26] of one representative compound (**5a**) is provided in the main manuscript.

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.07.052.

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25. *General synthetic procedure for preparation of 2-amino-5-isatinylidenethiazol-4-ones (**5**):* In a typical reaction a solution of isatin (1 mmol), rhodanine (1 mmol), amine (1.0 mmol) in EtOH–water (2+2 ml) were refluxed at 80–90 °C till completion using 40 mg of the catalyst (**4**). The completion of the reaction was indicated by the disappearance of the starting material in thin layer chromatography. After completion of the reaction the crude mixture was filtered, washed several times with water and then with ethanol. The residue contained both the product and the catalyst. Then the crude product was taken in DCM/MeOH (1:1 v/v) and again filtered to separate the product as filtrate. The solvent was removed in rotary evaporator and crude product was recrystallized from DCM/MeOH (1:1 v/v). The compounds (**5**) were characterized by IR, $^1H$ NMR, $^{13}C$ NMR and CHN and X-ray single crystal analysis.
26. *1-Allyl-3-(4-oxo-2-piperidin-1-yl-4H-thiazol-5-ylidene)-1,3-dihydro-indol-2-one* ***5a***: Orange solid, mp 140–142 °C ($CH_2Cl_2$+EtOAc, equal volumes); IR (KBr): 3434, 3042, 2923, 1593, 1509, and 1333 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$: 8.97 (1H, d, $J$ = 7.8 Hz, aromatic-H), 7.09 (1H, t, $J$ = 7.5 Hz, aromatic-H), 6.89 (1H, t, $J$ = 7.8 Hz, aromatic-H), 6.59 (1H, d, $J$ = 7.8 Hz, aromatic-H), 5.72-5.66 (1H, m, =C*H*), 5.03–4.97 (2H, m, =C$H_2$), 4.19 (2H, d, $J$ = 5.1 Hz, allylic–C$H_2$), 3.80 (2H, br s, piperidine–C$H_2$), 3.41 (2H, br s, piperidine–C$H_2$), 1.52 (6H, br s, piperidine–C$H_2$); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$: 179.7, 176.3, 168.2, 143.1, 138.6, 131.1, 129.2, 125.1, 123.1, 120.6, 117.9, 108.6, 49.8, 49.7, 42.7, 26.3, 25.6, 23.9; Anal. Calcd for $C_{19}H_{19}N_3O_2S$: C, 64.57; H, 5.42; N, 11.89%. Found C, 64.76; H, 5.50; N, 11.99%.