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A convenient one-pot synthesis of thiazol-2-imines: application in the construction of pifithrin analogues

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Abstract

For the first time a reaction intermediate has been isolated giving further insight into the mechanism of thiazol-2-imine formation. The first step of the reaction requires a basic medium, while the second step is an acid mediated E1 elimination reaction. An efficient one-pot synthesis of substituted thiazol-2-imines have been achieved by the condensation of carbonyl compounds with thioureas and 1,3-disubstituted thioureas using 1,1′-(ethane-1,2-diyl)dipyridinium bistribromide (EDPBT). Unsymmetrical 1,3-disubstituted thioureas give regioselective products with symmetrical ketones, which are mainly governed by the pK_as of NH protons of thiourea, whereas symmetrical 1,3-disubstituted thioureas give regioselective products with symmetrical carbonyl compounds owing to the regioselective bromination of ketones. The methodology is extended to access novel neurodegenerative drug candidate pifithrin-α analogues in good yields in shorter reaction time. This method is simple, versatile and is applicable for different 1,3-disubstituted thioureas as well as a range of carbonyl compounds.

1. Introduction

The mechanism of thiazol-2-imine formation has not been well understood leading to the proposal of incorrect structures for the products by two independent research groups.[1,2] Recently, we have unequivocally demonstrated that the reaction of benzoyl-3-phenylthioureas with bromine/1,1′-(ethane-1,2-diyl)dipyridinium bistribromide (EDPBT) and either acetone or enolizable ketones in the presence of triethylamine gives thiazol-2-imine derivatives and not imidazol-2-thione as reported earlier.[3,4] Further, we have established that even in aqueous media the course of the reaction remains unaltered giving thiazol-2-imine derivatives instead of imidazol-2-thiones as reported.[2,4]

Over the last decade attempts have been made to replace the corrosive and toxic bromine with various ammonium tribromides viz. tetrabutylammonium tribromide for various synthetically useful organic transformations.[5,6] A better ammonium ditribromide reagent 1,1′-(ethane-1,2-diyl)dipyridinium bistribromide (EDPBT) has been developed in our laboratory, which is far superior than the other reagents in terms of its stability, selectivity and higher bromine content.[7]

The thiazolidene-2-imine[3] or thiazol-2-imine[4] or 2-imino-thiazoline[15,18,23d,25a] ring system as it has been named by different groups is present in several drug candidates possessing interesting biological activities such as muscarinomimetic, antimycotic, hypolipemic, antidiabetic, thrombopoietin agonism, cell adhesion antagonists, platelet GPIIb/IIIa receptor antagonists, anti-inflammatory, analgesic and kinase (CDK1,CDK5 and GSK3) inhibition, schistosomicides, cadiotonics and trichomonides.[8] Thiazoline derivatives have found interesting applications in agriculture as acricides, insecticides and plant growth regulators.[9] Recently, 2-imino-thiazolines were found to have antifungal activity[10] and skin whitening properties.[11]

The basic 2-aminothiazole moiety was first synthesized by a Hantzsch condensation reaction involving thiourea and α-haloketone.[12] This approach was subsequently adopted for the synthesis of *N*-alkylated imino-thiazolines by replacing thioureas with mono-*N*-substituted thioureas.[13] Several alternative

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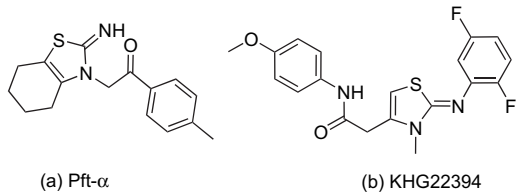


Figure 1. Structures of pharmacologically important molecules: (a) p53 inactivator; (b) skin whitening agent.

strategies have been devised, which include N-alkylation of aminothiazoles,[8c,14] potassium thiocyanate treatment of α-bromoketimines,[15] reaction of *N*-monoalkylated thioureas with 3-bromomethyl-2-cyanocinnamonitrile,[16] cycloadditions followed by elimination of 5-imino-1,2,4-thiazolidin-3-ones with enamines and ester enolate,[17] ring transformation of 1-arylmethyl-2-(thiocyanomethyl)aziridines in the presence of $TiCl_4$ and acylchloride,[18] reaction of *N*-propargylaniline with acylisothiocyanates,[19] and phenylamino acetonitrile with alkyl isothiocyanates.[20] Less general approaches towards the synthesis of these heterocycles involve the reaction of ketone either with *N*-alkyl rhodanamine or bisbenzyl formamidine disulfide[21] or the reaction of α-chloroketones with thiosemicarbazide in an acidic medium,[22] condensation of α-haloketones with *N*-benzoyl-*N*′-arylthioureas or *N*,*N*′-disubstituted thioureas.[23,24]

Pifithrin (Pft-α) (Fig. 1), isolated by screening of chemical libraries having 2-imino-thiazoline skeleton, is the lead compound of p53 inactivators and have received increasing attention due to its possible applications in several major neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, stroke, cancer therapy and other pathologies related to various signalling pathways.[25]

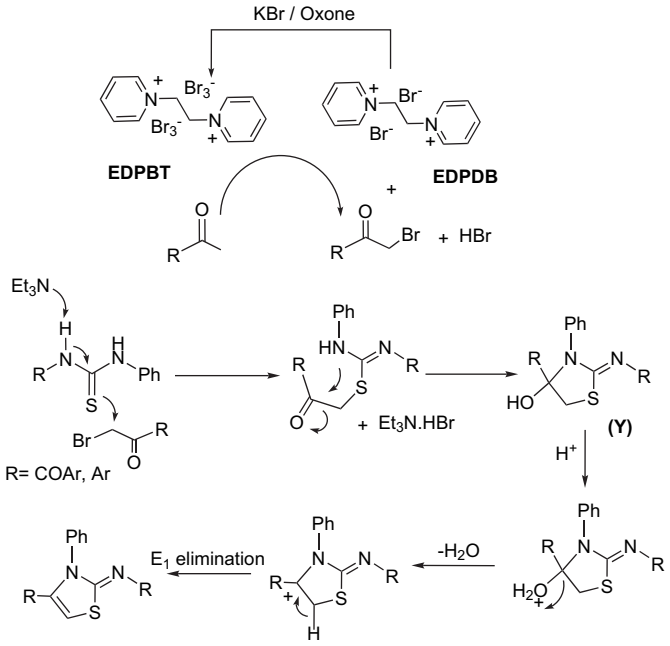
Although some of the methods of preparation of thiazol-2-imines are effective, the drawbacks associated with most of the procedures reported in the literature require arduous preparation of precursor substrates, difficulties in workup and isolation, the need for harsh reaction conditions, low yields and long reaction times. The use of lachrymatory α-haloketones is unavoidable for methods using thioureas as starting materials. There are only two reports on the one-pot procedure for the synthesis of 2-iminothiazoline involving *N*,*N*′-dialkylthiourea and in situ generated α-bromoketones, which is limited to only symmetrical thioureas and few selected ketones.[26] Methods using thioureas are limited to symmetrical thioureas and few selected ketones only thus lacking regioselectivity in 2-iminothiazoline formation. The important drugs, pifithrin (Pft-α) analogues, have been prepared under a harsh reaction condition and at longer reaction times giving lesser yields. In this manuscript we have revisited the reaction mechanism and developed a one-pot synthesis of thiazol-2-imine derivatives, and the synthetic methodology was applied towards the synthesis of novel drug candidate pifithrin-α and its analogues.

2. Results and discussion

The genesis of the work started with the two earlier reports proposing wrong reaction mechanism for the reaction of benzoylthioureas and α-haloketones, which ultimately led to the wrong interpretation of the structures of the products involved.[1,2] In order to further delineate our objective we reinvestigated both the reactions[1,2] using our newly developed bromine equivalent reagent, 1,1′-(ethane-1,2-diyl)dipyridinium bistribromide (EDPBT).[6i,7] The reagent EDPBT is capable of brominating enolizable ketones[7] as well as generating 2 equiv of HBr, 1 equiv during bromination of ketone and the second equivalent by the nucleophilic displacement of bromide by sulfur thereby making the medium acidic even in the presence of 1 equiv of triethylamine (Scheme 1). An acidic medium facilitates the dehydration of the intermediate tertiary alcohol. This prompted us to develop a one-pot procedure for the synthesis of thiazol-2-imine derivative from benzoylphenylthioureas and enolizable ketones.

The in situ generated α-bromoacetone obtained by the reaction of acetone with 1,1′-(ethane-1,2-diyl)dipyridinium bistribromide (EDPBT) reacts with a solution of 1-benzoyl-3-phenyl-thiourea **1** giving product **1a** in 78% isolated yield. The product **1a** obtained was found to be identical (melting point, IR, ^1H and ^{13}C NMR) to that of the product obtained earlier by Zou and by us using molecular bromine.[1,3,4] The structure of **1a** has already been confirmed as having the thiazol-2-imine skeleton by X-ray crystallographic analysis.[3] The requirement of an inert atmosphere using bromine by Zou et al. is really not necessary when bromine is replaced with EDPBT and the reaction works even under a moist condition.

As speculated earlier, this reagent brominates enolizable ketones to α-bromoketones. The carbon of the bromomethyl group is attacked by sulfur of thiourea, which is facilitated due to the abstraction of the NH proton flanked by a carbonyl and a thiocarbonyl moiety leading to the intermediate tertiary alcohol.[3] However, the Kaupp group has proposed an ionic intermediate with thiocarbenium and alkyl ammonium



Scheme 1. Proposed reaction mechanism of thiazol-2-imine formation.

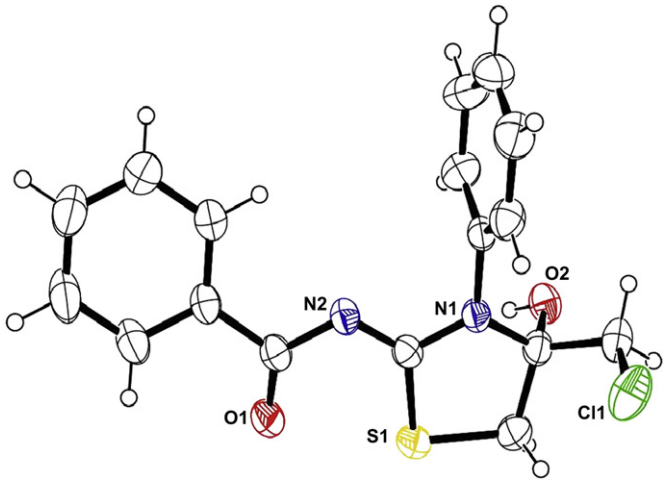


Figure 2. An ORTEP view with the atomic numbering scheme of (**Y**).

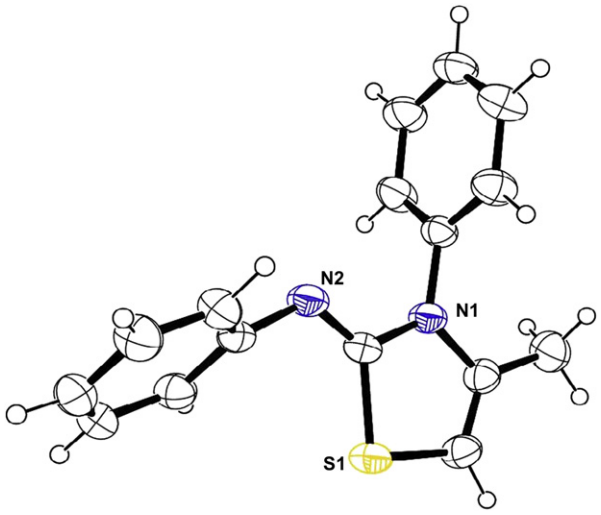
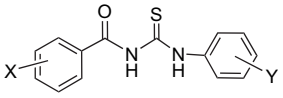
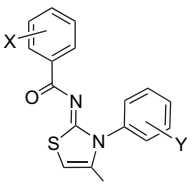


Figure 3. An ORTEP view with the atomic numbering scheme of **7a**.

intermediate (thiazolium) species. We differ with the mechanism proposed by Manaka[23f] and by Kaupp[23i] in the sense that due to the higher acidity of the NH proton, it would prefer to exist as isothiourea rather than as thiocarbenium ion and that the thiazolium salt should exist as thiazol-2-imine. Further, the elimination of the intermediate tertiary alcohol is not by a base catalyzed E2 mechanism, rather it should be by an E1 mechanism. This assumption of ours is confirmed by isolation of the intermediate 1-benzoyl(4-hydroxy-3,4-diphenylthiazolylidene)2-imine, obtained by the reaction of benzoylthiourea **1** (1 equiv) and acetophenone (1 equiv) in the presence of EDPBT (0.5 equiv) and triethylamine (4 equiv).[3] The intermediate 1-benzoyl(4-hydroxy-3,4-diphenylthiazolylidene)-2-imine obtained was identical to the product obtained earlier.[3] When 1,3-dichloroacetone (1 equiv) was reacted with benzoylthiourea **1** (1 equiv) in the presence of triethylamine (2 equiv) a solid product (**Y**) (Scheme 1) was obtained after usual workup. Crystallisation of the compound from ethyl acetate/hexane (4:1) gave a colourless crystal. X-ray crystallographic analysis of the compound revealed the presence of thiazol-2-imine skeleton as shown in Figure 2.

Table 1
Reaction[a] of benzoylthioureas with acetone and EDPBT

Substrate	Product	Yield[b] (%)
		
X=H, Y=H (**1**)	X=H, Y=H (**1a**)	78
X=H, Y=*p*(Cl) (**2**)	X=H, Y=*p*(Cl) (**2a**)	72
X=H, Y=*p*(Me) (**3**)	X=H, Y=*p*(Me) (**3a**)	82
X=H, Y=*o*(Cl) (**4**)	X=H, Y=*o*(Cl) (**4a**)	68
X=H, Y=*p*(Br) (**5**)	X=H, Y=*p*(Br) (**5a**)	68
X=*m*(Br), Y=H (**6**)	X=*m*(Br), Y=H (**6a**)	85

[a] Reactions were monitored by TLC.
[b] Isolated yields.

The NH proton flanked by a carbonyl and a thiocarbonyl is sufficiently acidic and its deprotonation by triethylamine is feasible and is essential as it enhances the nucleophilicity of sulfur towards the attack on bromomethyl ketone forming an imine derivative. The distance between C(3)–N(3) is 1.308 Å, which is typical of an imine C–N double bond. Surprisingly, many earlier reports have proposed a base catalyzed E2 type elimination. This isolated intermediate (**Y**) is stable under basic and neutral conditions. Treatment of the intermediate (**Y**) with dilute (HCl) led to the formation of thiazol-2-imine with elimination of water, hence a base catalyzed elimination is completely ruled out. The hydroxyl group being tertiary in nature is only susceptible to acid catalyzed E1 elimination. It may be mentioned here that the use of 1 equiv of triethylamine does not make the medium basic for an E2 elimination rather the medium remains acidic by just neutralizing one of the two equivalents of HBr generated in the medium (Scheme 1).

Having successfully established the mechanism of the reaction, our next objective was to apply this methodology to various other benzoylthioureas. When benzoylthiourea **2** was

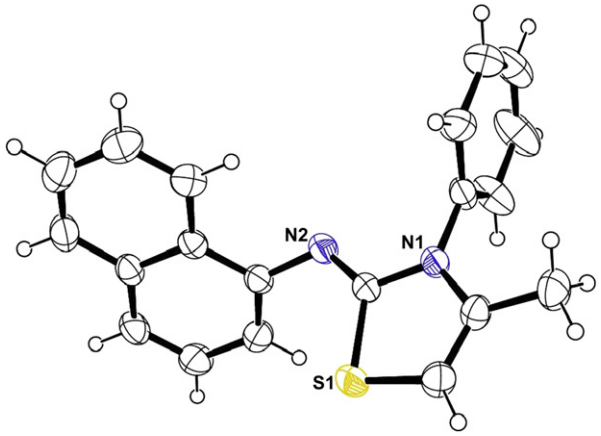


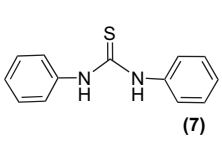
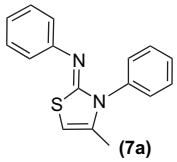
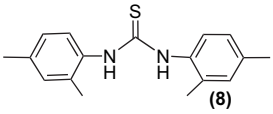
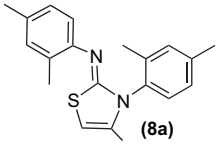
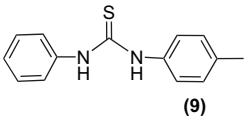
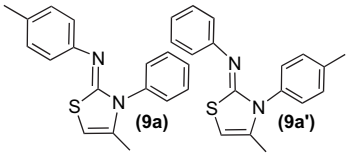
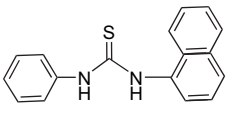
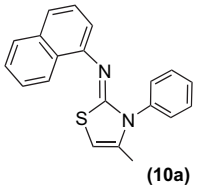
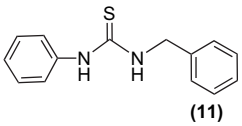
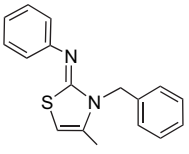
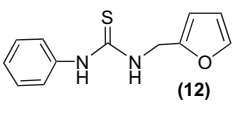
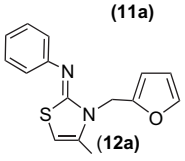
Figure 4. An ORTEP view with the atomic numbering scheme of **10a**.

reacted under identical conditions as described above, the product **2a** obtained was again found to be identical (melting point, IR, ^{1}H and ^{13}C NMR) to that of the product obtained earlier by Wang group[2] and also by us in an aqueous medium.[4] The structure of **1b** was already confirmed as having the thiazol-2-imine or thiazolimine skeleton by X-ray crystallographic analysis.[4] Thus the course of the reaction and the reaction mechanism remain unchanged both in the organic and in the aqueous media. Benzoylthioureas **3**, **4** and **5** gave their corresponding thiazol-2-imine products **3a**, **4a** and **5a**, respectively (Table 1). Thiazol-2-imine ring formation is general and not specific to a particular benzoylthiourea. When 3-bromobenzoyl-3-phenylthiourea **6** was reacted under the above conditions it gave the corresponding thiazol-2-imine derivative **6a**. The product obtained was again found to be identical (melting point, IR, ^{1}H and ^{13}C NMR) to that of the product obtained earlier by Zou group and independently by us.[1,3] The presence of thiazol-2-imine skeleton has been confirmed by X-ray crystallographic analysis.[3] It may be noted here that X-ray crystal structures of **1a**, **2a** and **6a** all revealed having *syn*-stereochemistry. The *syn* selectivity is likely due to the steric hindrance of the acyl group and the *N*-phenyl group. This observation is consistent with the observations made by others.[8d,23f]

The acidity of the NH proton of 1,3-disubstituted thiourea is expected to be less than the NH proton of benzoylthiourea. Having effectively applied to different benzoylthioureas we wished to test if this methodology can be applied to 1,3-diaryl thiourea as well. When 1,3-diphenyl thiourea **7** was reacted under an identical condition to that described above for benzoylthioureas a solid product was obtained. The ORTEP diagram with atom numbering scheme of **7a** is shown in Figure 3. X-ray crystallographic analysis of the product **7a** again revealed the presence of thiazol-2-imine skeleton. The proposed reaction mechanism for 1,3-disubstituted thiourea is expected to be similar to the one proposed for benzoylthiourea.[3]

This methodology was successfully applied to another 1,3-disubstituted symmetrical thiourea **8** giving corresponding product **8a** in good yield. In order to study the regioselectivity, unsymmetrical thiourea 1-phenyl-3-*p*-tolyl-thiourea **9** was reacted under identical condition. The product obtained was an equimolar mixture of **9a** and **9a′** indicating the equal ease of thiazol-2-imine formation from either side of the thiourea since the acidity of both NH protons is similar. However, when naphthyl ring is attached to one of the sides in thiourea it results in exclusive regioselective product **10a** obtained via deprotonation of the NH proton from the naphthyl side of the urea **10**. The structure of the product **10a** was confirmed by X-ray crystallographic analysis. The ORTEP diagram with atom numbering scheme of product **10a** is shown in Figure 4. Formation of regioselective product **10a** is because of the higher acidic character of the naphthyl NH proton. The measured pK_as of 1-naphthylamine and aniline are 3.94 and 4.61, respectively (Table 2).

Table 2
Reaction[a] of 1,3-disubstituted thiourea with acetone and EDPBT

Substrate	Product	Yield[b] (%)
 (7)	 (7a)	75
 (8)	 (8a)	78
 (9)	 (9a) (9a')	82
 (10)	 (10a)	72
 (11)	 (11a)	69
 (12)	 (12a)	66

[a] Reactions were monitored by TLC and stopped after 1.5 h.
[b] Isolated yields.

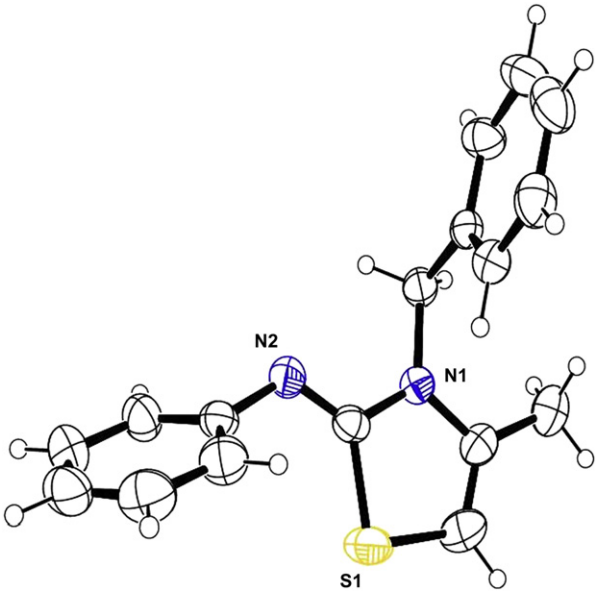
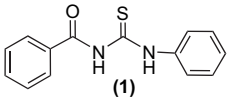
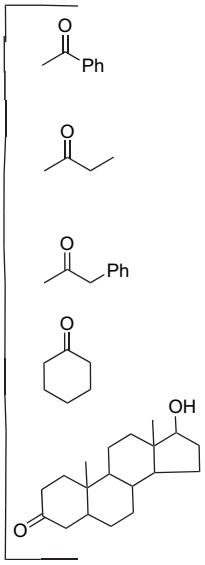
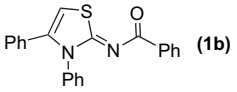
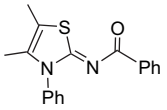
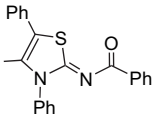
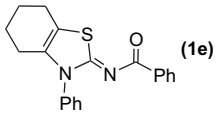
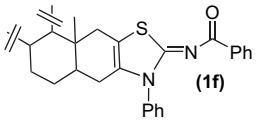
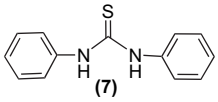
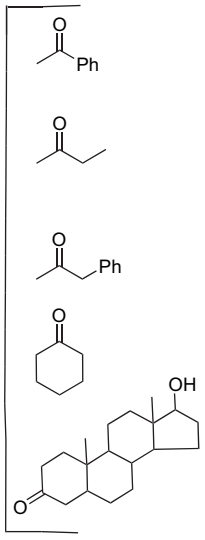
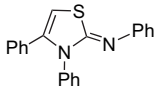
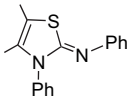
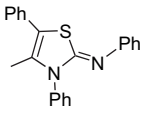
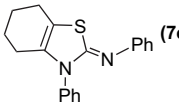
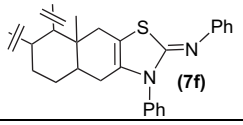


Figure 5. An ORTEP view with the atomic numbering scheme of **11a**.

Table 3
Reaction[a] of 1,3-disubstituted thiourea with ketone and EDPBT

Substrate	Ketone	Product	Yield[b] (%)
 (1)		 (1b)	77
		 (1c)	68
		 (1d)	71
		 (1e)	65
		 (1f)	48[c]
 (7)		 (7b)	82
		 (7c)	69
		 (7d)	66
		 (7e)	70
		 (7f)	45[c]

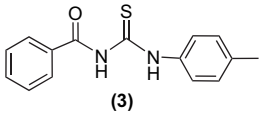
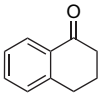
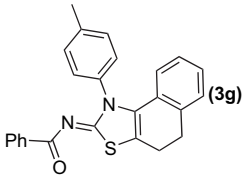
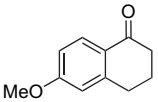
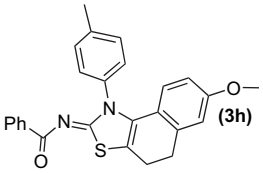
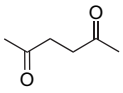
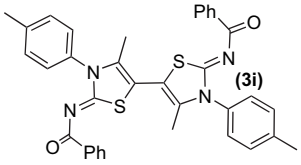
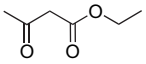
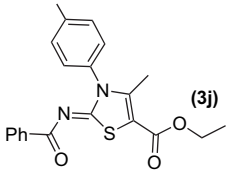
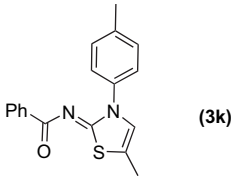
[a] Reactions were monitored by TLC and stopped after 1.5 h.
[b] Isolated yields.
[c] Reaction was continued up to 6 h.

However, for substrates possessing phenylic and benzylic systems as in the case of 1-benzyl-3-phenyl-thiourea **11**, the NH proton flanked by a phenyl and a thiocarbonyl moiety is more acidic compared to the other NH protons flanked by a benzyl and a thiocarbonyl group giving product **11a** obtained by the deprotonation from the phenyl side of the thiourea. This is because of the higher basicity of the benzyl amine (pK_a 9.41) compared to aniline (pK_a 4.61). The structure of product **11a** is confirmed by single crystal X-ray analysis. The ORTEP diagram with atomic numbering scheme of **11a** is shown in Figure 5.

The ease of deprotonation from the phenyl side of the NH proton compared to the benzylic side leading to the formation of thiazol-2-imine skeleton is demonstrated for substrate **12** containing a furyl ring attached to one side.

So far the formation of thiazol-2-imine is applied to various benzoylthioureas and 1,3-disubstituted thioureas with acetone only. This approach can be applied to various other ketones as shown in Table 3. Substrate 1-benzoyl-3-phenyl-thiourea **1** was reacted with acetophenone under an identical reaction condition and the product obtained **1b** was found to be identical (melting point, IR, ^{1}H and ^{13}C NMR) to that of the product

Table 4
Reaction[a] of 1-benzoyl-3-*p*-tolyl-thiourea **3** with various ketones

Substrate	Ketone	Product	Time	Yield[b] (%)
 (3)		 (3g)	1.5	73
		 (3h)	1.5	75
		 (3i)	2.0	55[c]
		 (3j)	1.5	78
		 (3k)	1.0	68

[a] Reactions were monitored by TLC.
[b] Isolated yields.
[c] 0.5 equiv of 2,4-hexan-dione was used.

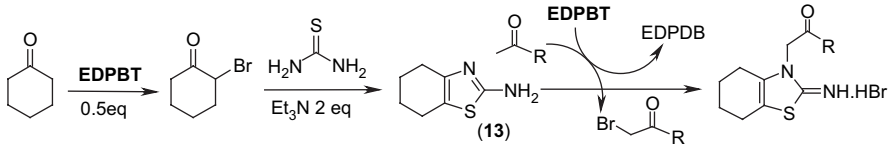
obtained earlier by Zou and by us using molecular bromine.[1,3] The structure of product **1b** has already been confirmed as having the thiazol-2-imine skeleton by X-ray crystallographic analysis.[3] Unsymmetrical ketones such as butan-2-one and 1-phenyl-propan-2-one gave products corresponding to the α-bromination at the highly substituted side of the ketones with EDPBT finally leading to the formation of regioselective heterocycles thiazol-2-imine **1c** and **1d**, respectively. Cyclohexanone with 1-benzoyl-3-phenyl-thiourea **1** gave the product **1e**. Interestingly, anabolic thiazoloandrostane **1f**[27] was prepared from 17α-methyl-5α-androstan-17β-ol-3-one in moderate yield. The reactivity of 1,3-diphenyl thiourea **7** is similar to 1-benzoyl-3-phenyl-thiourea **1** as shown in Table 3.

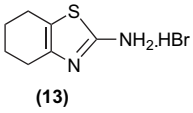
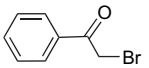
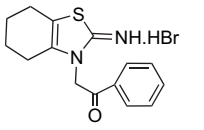
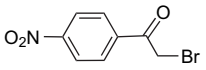
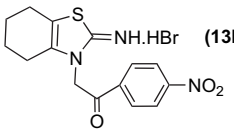
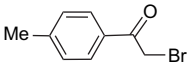
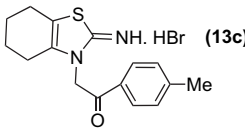
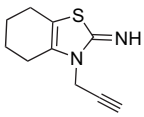
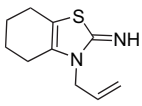
The successful applications of the methodology to various ketones prompted us to test the usefulness of this synthetic strategy on other ketones and diketones. The in situ generated α-brominated products of cyclic ketones such as 1-tetralone and 6-methoxy-1-tetralone with EDPBT react with 1-benzoyl-3-(*p*-tolyl)-thiourea **3** giving thiazol-2-imine products **3g** and **3h** in good yields. The synthetic utility of this method is demonstrated in the synthesis of bis-thiazoline product using a 1,4-diketone. Treatment of hexan-2,5-dione with 1 equiv of EDPBT possibly gave dibromo product 3,4-dibromo-hexan-2,5-dione in the reaction medium, which reacts with thiourea **3** giving bis-thiazol-2-imine product **3i** in 55% isolated yield. Finally, ethylacetoacetate under the present experimental condition gave regioselective product **3j**, which is in accordance with the reported one.[23f]

The synthetic utility of this reagent EDPBT and the methodology was finally demonstrated for the syntheses of neurodegenerative drug pifithrin-α and its analogues. Even though there are some reports for the syntheses of pifithrin analogues, almost all the reported methods use a two-step strategy. The first stage involves the iodine mediated formation of aminothiazole by the reaction of cyclic ketones and thiourea at 110 °C for 12 h. The product after isolation is then reacted with alkyl halide to give pifithrin-α analogues with an overall yield in the range of 30–35%.[25a,25d] This method suffers due to high reaction temperatures, longer reaction times and less yields (Table 4).

As pifithrin-α analogues are very important scaffolds in medicinal chemistry, we have applied this methodology to access these biologically important compounds. The in situ generated

Table 5
Reaction[a] of in situ generated aminothiazole with various α-haloketones and alkyl bromides



Substrate	α-Haloketone/alkyl halide	Product	Time (h)	Yield[b] (%)
 (13)		 (13a)	4.5	62
		 (13b)	4.0	54
		 (13c)	4.5	57
		 (13d)	6.0	66[c]
		 (13e)	6.0	60[c]

[a] Reactions were monitored by TLC.
[b] Isolated yields.
[c] Propargyl and allyl bromides used were from commercial source and not generated in situ.

α-bromocyclohexanone obtained by the reaction of cyclohexanone and EDPBT in acetonitrile reacts with thiourea to give aminothiazole. α-Bromoacetophenone prepared from acetophenone using EDPBT in acetonitrile[7] was added to the above reaction medium containing aminothiazole and triethylamine. The pifithrin analogue **13a** was obtained in 62% overall isolated yield. The pifithrin **13c** and its analogues **13b** were prepared using *p*-methylacetophenone and *p*-nitroacetophenone, respectively. Similarly, other analogues **13d** and **13e** were also prepared using propargyl and allyl bromide showing the versatility of this method. Thus, the present method is superior to any of the reported procedure in terms of simplicity and better yield (Table 5).

3. Conclusion

In conclusion, we have isolated the reaction intermediate and characterized it by X-ray crystallography. Formation of thiazol-2-imine is a two-step process, the first step of the reaction requires the medium to be basic for favorable nucleophilic attack and the intermediate tertiary alcohol is stable under both neutral and basic conditions. The second step of the reaction is an acid mediated E1 elimination. We have achieved an efficient one-pot synthesis of substituted thiazol-2-imines by the condensation of carbonyl compounds with thioureas and 1,3-disubstituted thioureas using EDPBT. The pK_as of the NH protons of thioureas dictate the regioselectivity in the case of symmetrical ketones. The regioselective bromination at the more substituted side in the case of unsymmetrical ketones produces regioselective product with symmetrically 1,3-disubstituted thioureas. Bis-thiazoline derivative can be prepared from dicarbonyl compound. Neurodegenerative drugs pifithrin-α and its analogues have been successfully prepared employing this methodology. The pifithrin analogues obtained by this one-pot method is by far the best in terms of shorter reaction time and better yield. This method is simple, versatile and can be applied successfully for different 1,3-disubstituted thioureas as well as a range of carbonyl compounds.

4. Experimental

4.1. General information

All the reagents were of commercial grade and purified according to the established procedures. Organic extracts were dried over anhydrous sodium sulfate. Solvents were removed in a rotary evaporator under reduced pressure. Silica gel (60–120 mesh size) was used for the column

chromatography. Reactions were monitored by TLC on silica gel 60 F_{254} (0.25 mm). NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 with tetramethylsilane as the internal standard for ^1H NMR (400 MHz) and $CDCl_3$ or DMSO-d_6 solvent as the internal standard for ^{13}C NMR (100 MHz). HRMS spectra were recorded using WATERS MS system, Q-Tof premier and data analyzed using Mass Lynx4.1. Melting points were recorded on Buchi B-545 melting point apparatus and are uncorrected. IR spectra were recorded in KBr or neat on a Nicolet Impact 410 spectrophotometer.

4.2. Crystallographic description

Crystal data were collected with Bruker Smart Apex-II CCD diffractometer using graphite monochromated Mo Kα radiation (λ=0.71073 Å) at 298 K. Cell parameters were retrieved using SMART[28] software and refined with SAINT[28] on all observed reflections. Data reduction was performed with the SAINT software and corrected for Lorentz and polarization effects. The structure was solved by direct methods implemented in SHELX-97[29] program and refined by full-matrix least-squares methods on F^2. All non-hydrogen atomic positions were located in difference Fourier maps and refined anisotropically. The hydrogen atoms were placed in their geometrically generated positions. All the colourless crystals were isolated in rectangular shape from absolute ethanol at room temperature. CCDC numbers for compounds **Y**, **7a**, **10a**, and **11a** are CCDC 652469, CCDC 652470, CCDC 652472 and CCDC 652473, respectively. These data can be obtained from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

4.3. Preparation of N-benzoyl(4-(chloromethyl)-4-hydroxy-3-phenylthiazolidine)-2-imine (**Y**)

To a solution of 1-benzoyl-3-phenyl-thiourea **1** (0.256 g, 1 mmol) in acetonitrile (2 mL) containing triethylamine (0.202 g, 2 mmol) was added a solution of 1,3-dichloroacetone (0.128 g, 1 mmol) in acetonitrile (2 mL). The reaction was completed within 1 h as can be judged from TLC. After completion of the reaction, solvent was evaporated and admixed with ethyl acetate (20 mL). The ethyl acetate layer was washed with a saturated solution of $NaHCO_3$ (5 mL), dried over anhydrous Na_2SO_4, concentrated under reduced pressure and purified over a silica gel column (25% EtOAc/hexane) to give 85% of the product **Y**. Compound **Y** was recrystallized from a mixture of EtOAc/hexane (8:2) to give colourless needle like crystals. Mp 137–138 °C. R_f (25% EtOAc/hexane) 0.31. δ_H (400 MHz, $CDCl_3$): 3.04 (d, 1H, J=12.8 Hz), 3.55 (d, 2H, J=12.8 Hz), 3.78 (d, 1H, J=12.8 Hz), 6.01 (br s, 1H), 7.10–7.65 (m, 7H), 7.85 (d, 1H, J=7.2 Hz), 7.93 (d, 2H, J=7.2 Hz). δ_C (100 MHz, $CDCl_3$): 37.9, 46.9, 92.7, 120.6, 127.3, 128.3, 129.0, 129.3, 130.1, 132.6, 137.2, 174.0, 177.5. ν_{max} (KBr): 3334, 3191, 3165, 3063, 2945, 2848, 1655, 1609, 1486, 1025, 702 cm^{-1}. $C_{17}H_{15}ClN_2O_2S$ (346.84): calcd C 58.87, H 4.36, N 8.08, S 9.24; found C 58.93, H 4.41, N 8.01, S 9.18; HRMS (ESI): MH^+, found 346.8364, $C_{17}H_{15}$ Cl N_2O_2S requires 346.8369.

Crystallographic description of **Y**: crystal dimension (mm): 0.48×0.27×0.19; $C_{17}H_{14}ClN_2O_2S$, M_r=345.83; triclinic, space group P_1; a=11.3616(3) Å, b=12.2735(2) Å, c=14.1624(2) Å; α=114.3440(10), β=104.7900(10), γ=99.1230(10), V=1659.86(6) (Å^3); Z=4; ρ_{cal}=1.320 mg/m^3; μ (mm^{-1})=0.358; F (000)=684; reflections collected/unique=15,148/3901; refinement method=full-matrix least-squares on F^2; final R indices [$I>2\sigma_I$] R_1=0.0419, $wR2$=0.0940, R indices (all data) $R1$=0.0671, $wR2$=0.1067; goodness-of-fit=1.024.

4.4. General experimental procedure I: preparation of 2-benzoylimino-4-methyl-3-phenyl-3H-thiazole (**1a**) using EDPBT

To a solution of 1,1′-(ethane-1,2-diyl)dipyridinium bistribromide (EDPBT) (0.333 g, 0.5 mmol) in acetonitrile (2 mL) was added acetone (0.116 g, 2 mmol) and stirring continued for 10 min. During this period, the bromination of acetone was complete as judged from the disappearance of the orange colour of EDPBT. The supernatant containing the bromoketone was then directly filtered into a solution of 1-benzoyl-3-phenyl-thiourea **1** (0.256 g, 1 mmol) in acetonitrile (2 mL) containing triethylamine (0.101 g, 1 mmol) and kept at 60 °C. The reaction was completed within 1 h as can be judged from TLC. After completion of the reaction, solvent was evaporated and admixed with ethyl acetate (20 mL). The ethyl acetate layer was washed with a saturated solution of $NaHCO_3$ (5 mL), dried over anhydrous Na_2SO_4, concentrated under reduced pressure and purified over a silica gel column (25% EtOAc/hexane) to give 78% of the product **1a**.

4.5. General procedure II: preparation of pifithrin-α analogues

To a solution of cyclohexanone (2 mmol) in acetonitrile (2 mL) was added 1,1′-(ethane-1,2-diyl)dipyridinium bistribromide (EDPBT) (0.666 g, 1 mmol) and the reaction stirred for 10 min. This reaction mixture was then filtered into a solution of thiourea (0.152 g, 2 mmol), triethylamine (0.202 g, 2 mmol) in acetonitrile (5 mL) and was heated at 80 °C for 5 h to give aminothiazole hydrobromide. The free aminothiazole was obtained by treating it with triethylamine (0.202 g, 2 mmol). Separately, acetophenone (0.240 g, 2 mmol) was brominated with EDPBT (0.666 g, 1 equiv) using our solvent free method to give bromoacetophenone.[8] The bromoacetophenone was added to crude aminothiazole and the reaction mixture was stirred for 4.5 h. The desired product precipitated out from the reaction mixture was filtered and washed with acetonitrile to obtain the pure product. Products **13d** and **13e** were isolated as their free base by sodium carbonate workup.

4.6. Spectral data for selected compounds

4.6.1. 2-Benzoylimino-3-phenyl-4-methyl-3H-thiazole (**1a**)

White needles, R_f (25% EtOAc/hexane) 0.38, mp 156–157 °C. δ_H (400 MHz, $CDCl_3$): 2.05 (s, 3H), 6.39 (s, 1H), 7.31 (m, 5H), 7.54 (m, 3H), 8.01 (m, 2H). δ_C (100 MHz, $CDCl_3$):

15.2, 104.7, 128.0, 128.2, 128.5, 129.4, 129.6, 131.5, 134.5, 137.0, 137.6, 170.2, 174.5. ν_{max} (KBr): 3050, 2948, 1598, 1564, 1491, 1458, 1364, 1342, 1275, 1171, 1066, 1017, 903 cm^{-1}. $C_{17}H_{14}N_2OS$ (294.38): calcd C 69.36, H 4.79, N 9.52, S 10.89; found C 69.47, H 4.81, N 9.47, S 10.78. HRMS (ESI): MH^+, found 295.0883, $C_{17}H_{14}N_2OS$ requires 295.0905.

*4.6.2. 2-Benzoylimino-3-(4-chloro-phenyl)-4-methyl-3H-thiazole (**2a**)*

White needles, R_f (25% EtOAc/hexane) 0.27, mp 199–201 °C. δ_H (400 MHz, $CDCl_3$): 2.04 (s, 3H), 6.37 (s 1H), 7.40 (m, 5H), 7.55 (d, 2H, J=7.6 Hz), 8.03 (d, 2H, J=7.6 Hz). δ_C (100 MHz, $CDCl_3$): 15.1, 104.9, 128.1, 129.3, 129.6, 129.8, 131.6, 134.0, 135.2, 135.9, 136.7, 170.1, 174.4. ν_{max} (KBr): 3054, 2912, 1599, 1561, 1489, 1459, 1344, 1270, 902, 705 cm^{-1}. $C_{17}H_{13}ClN_2OS$ (328.82): calcd C 62.10, H 3.99, N 8.52, S 9.75; found C 62.17, H 4.04, N 8.47, S 9.71. HRMS (ESI): M^+, found 328.8215, $C_{17}H_{13}ClN_2OS$ requires 328.8207.

*4.6.3. 2-Benzoylimino-3-(2-chlorophenyl)-4-methyl-3H-thiazole (**4a**)*

White solid, R_f (25% EtOAc/hexane) 0.51, mp 132–133 °C. δ_H (400 MHz, $CDCl_3$): 1.99 (s, 3H), 6.37 (s, 1H), 7.42 (m, 7H), 7.98 (d, 2H, J=8.4 Hz). δ_C (100 MHz, $CDCl_3$): 14.3, 104.4, 127.9, 128.0, 129.3, 130.1, 130.5, 130.9, 131.4, 132.6, 133.8, 135.1, 136.8, 169.7, 174.4. ν_{max} (KBr): 3065, 2917, 1602, 1566, 1481, 1344, 1281, 908, 716, 705 cm^{-1}. $C_{17}H_{13}ClN_2OS$ (328.82): calcd C 62.10, H 3.99, N 8.52, S 9.75; found C 62.38, H 4.08, N 8.31, S 9.78. HRMS (ESI): MH^+, found 328.9611, $C_{17}H_{13}ClN_2OS$ requires 328.9605.

*4.6.4. 2-(3-Bromobenzoylimino)-4-methyl-3-phenyl-3H-thiazole (**6a**)*

White needles, R_f (25% EtOAc/hexane) 0.41, mp 140–142 °C. δ_H (400 MHz, $CDCl_3$): 2.06 (s, 3H), 6.40 (s, 1H), 7.17 (t, 1H, J=8.0 Hz), 7.32 (d, 2H, J=7.6 Hz), 7.54 (m, 4H), 7.93 (d, 1H, J=6.8 Hz), 8.15 (s, 1H). δ_C (100 MHz, $CDCl_3$): 15.2, 104.9, 122.2, 127.9, 128.1, 128.5, 129.6, 129.7, 132.5, 134.2, 134.7, 137.3, 139.1, 170.3, 172.9. ν_{max} (KBr): 3086, 2923, 1596, 1557, 1496, 1459, 1450, 1337, 1255, 1127, 1033, 907, 739 cm^{-1}. $C_{17}H_{13}BrN_2OS$ (373.27): calcd C 54.70, H 3.51, N 7.50, S 8.59; found C 54.80, H 3.47, N 7.48, S 8.55. HRMS (ESI): MH^+, found 374.2857, $C_{17}H_{13}BrN_2OS$ requires 374.2809.

*4.6.5. 3-(2′,4′-Dimethylphenyl)-2-(2′,4′-dimethyl-phenylimino)-4-methyl-3H-thiazole (**8a**)*

White needles, R_f (25% EtOAc/hexane) 0.76, mp 134–135 °C. δ_H (400 MHz, $CDCl_3$): 1.76 (s, 3H), 2.07 (s, 3H), 2.24 (s, 3H), 2.26 (s, 3H), 2.36 (s, 3H), 5.57 (s, 1H), 6.93 (m, 6H). δ_C (100 MHz, $CDCl_3$): 15.3, 17.7, 17.9, 21.1, 21.4, 93.2, 120.7, 127.4, 128.1, 129.2, 130.1, 131.4, 132.1, 132.4, 134.2, 135.0, 136.9, 139.1, 148.7, 159.8. ν_{max} (KBr): 3056, 2912, 1615, 1585, 1497, 1358, 861, 749 cm^{-1}. $C_{20}H_{22}N_2S$ (322.48): calcd C 74.49, H 6.88, N 8.69, S 9.94; found C 74.26, H 6.93, N 8.75, S 9.89.

*4.6.6. 4-Methyl-3-phenyl-2-(p-tolylimino)-3H-thiazole and 4-methyl-2-phenylimino-3-(p-tolyl)-3H-thiazole (**9a**+**9a′**)*

Reddish oil, R_f (25% EtOAc/hexane) 0.73. δ_H (400 MHz, $CDCl_3$): 1.82 (br s, 6H), 2.28 (s, 3H), 2.39 (s, 3H), 5.59 (m, 2H), 6.98 (m, 8H), 7.36 (m, 9H). δ_C (100 MHz, $CDCl_3$): 15.5, 20.9, 21.2, 92.9, 93.3, 121.4, 121.6, 121.7, 122.8, 122.9, 128.4, 128.6, 128.9, 129.1, 129.2, 129.5, 129.7, 129.8, 130.2, 132.1, 132.2, 134.9, 135.1, 137.6, 138.3, 149.5, 152.1, 160.9, 161.0. ν_{max} (KBr): 3027, 2920, 1621, 1574, 1506, 1356, 1296, 1244, 1167, 1112, 1037, 879, 696, 533 cm^{-1}. $C_{17}H_{16}N_2S$ (280.39): calcd C 72.82, H 5.75, N 9.99, S 11.44; found C 72.73, H 5.81, N 10.08, S 10.91.

*4.6.7. 4-Methyl-2-(1′-naphthylimino)-3-phenyl-3H-thiazole (**10a**)*

White cubes, R_f (25% EtOAc/hexane) 0.64, mp 128–129 °C. δ_H (400 MHz, $CDCl_3$): 1.89 (s, 3H), 5.65 (s, 1H), 7.19 (d, 1H, J=7.6 Hz), 7.47 (m, 9H), 7.78 (d, 1H, J=8 Hz), 7.98 (d, 1H, J=8 Hz). δ_C (100 MHz, $CDCl_3$): 15.8, 93.9, 115.0, 123.1, 124.0, 125.2, 126.2, 126.5, 128.0, 128.8, 128.9, 129.3, 130.0, 135.0, 135.1, 138.1, 148.5, 160.9. ν_{max} (KBr): 3043, 2916, 1620, 1600, 1567, 1492, 1359, 1264, 777, 695, 545 cm^{-1}. $C_{20}H_{16}N_2S$ (316.43): calcd C 75.92, H 5.10, N 8.85, S 10.13; found C 75.49, H 4.96, N 8.69, S 10.16.

*4.6.8. 3-Benzyl-4-methyl-2-phenylimino-3H-thiazole (**11a**)*

White needles, R_f (25% EtOAc/hexane) 0.62, mp 111–113 °C. δ_H (400 MHz, $CDCl_3$): 2.02 (s, 3H), 5.16 (s, 2H), 5.52 (s, 1H), 7.03 (m, 3H), 7.30 (m, 7H). δ_C (100 MHz, $CDCl_3$): 14.9, 47.2, 92.6, 121.7, 122.8, 126.8, 127.5, 128.8, 129.5, 135.1, 137.5, 151.6, 160.2. ν_{max} (KBr): 3060, 3021, 2923, 1610, 1577, 1358, 1220, 913, 768, 696 cm^{-1}. $C_{17}H_{16}N_2S$ (280.39): calcd C 72.82, H 5.75, N 9.99, S 11.44; found C 72.87, H 5.82, N 9.91, S 11.52.

*4.6.9. 3-(Furfuryl)-4-methyl-2-phenylimino-3H-thiazole (**12a**)*

Reddish oil, R_f (25% EtOAc/hexane) 0.65. δ_H (400 MHz, $CDCl_3$): 2.23 (s, 3H), 5.08 (s, 2H), 5.51 (s, 1H), 6.36 (t, 1H, J=2.8 Hz), 6.42 (d, 1H, J=3.6 Hz), 7.08 (m, 3H), 7.36 (m, 3H). δ_C (100 MHz, $CDCl_3$): 14.9, 40.6, 92.7, 108.8, 110.9, 121.8, 123.1, 129.6, 134.9, 142.2, 150.6, 151.7, 159.5. ν_{max} (KBr): 3056, 3027, 2924, 2954, 1614, 1580, 1488, 1396, 1317, 1221, 1189, 1146, 1067, 1011, 931, 801, 767, 747, 696 cm^{-1}. $C_{15}H_{14}N_2OS$ (270.36): calcd C 66.64, H 5.22, N 10.36, S 11.86; found C 66.73, H 5.34, N 10.21, S 12.41.

*4.6.10. 2-Benzoylimino-3,4-diphenyl-3H-thiazole (**1b**)*

White needles, R_f (25% EtOAc/hexane) 0.62, mp 181–183 °C. δ_H (400 MHz, $CDCl_3$): 6.70 (s, 1H), 7.12 (d, 2H, J=8.4 Hz), 7.23 (m, 6H), 7.33 (t, 2H, J=7.6 Hz), 7.39 (d, 3H, J=7.0 Hz), 8.10 (d, 2H, J=8.4 Hz). δ_C (100 MHz, $CDCl_3$): 107.6, 128.1, 128.5, 128.6, 128.9, 129.0, 129.4, 130.7, 131.6, 136.8, 137.7, 139.2, 170.0, 174.7. ν_{max} (KBr): 3064, 2927, 1598, 1566, 1492, 1466, 1450, 1435, 1337, 1279, 1200, 1166, 1024, 899, 713 cm^{-1}. $C_{22}H_{16}N_2OS$ (356.45): calcd C 74.13, H 4.52, N 7.86, S 9.00; found C 74.21, H 4.58, N 7.79, S 8.94.

HRMS (ESI): MH^+, found 357.4563, $C_{22}H_{16}N_2OS$ requires 357.4557.

4.6.11. 2-Benzoylimino-4,5-dimethyl-3-phenyl-3H-thiazole (**1c**)

White solid, R_f (25% EtOAc/hexane) 0.46, mp 128–130 °C. δ_H (400 MHz, $CDCl_3$): 1.95 (s, 3H), 2.28 (s, 3H), 7.31 (m, 5H), 7.54 (m, 3H), 8.01 (d, 2H, J=7.2 Hz). δ_C (100 MHz, $CDCl_3$): 12.1, 12.4, 115.0, 128.0, 128.2, 128.3, 129.0, 129.4, 129.6, 131.4, 137.1, 138.2, 168.4, 174.1. ν_{max} (KBr): 3054, 2923, 1596, 1558, 1481, 1349, 905, 713 cm^{-1}. $C_{18}H_{16}N_2OS$ (308.41): calcd C 70.10, H 5.23, N 9.08, S 10.40; found C 70.37, H 5.31, N 9.23, S 10.26.

4.6.12. 2-Benzoylimino-3,5-diphenyl-4-methyl-3H-thiazole (**1d**)

White crystalline solid, R_f (25% EtOAc/hexane) 0.70, mp 168–170 °C. δ_H (400 MHz, $CDCl_3$): 2.11 (s, 3H), 7.41 (m, 13H), 8.03 (d, 2H, J=6.8 Hz). δ_C (100 MHz, $CDCl_3$): 13.7, 120.5, 128.0, 128.2, 128.3, 129.1, 129.2, 129.3, 129.4, 129.6, 131.5, 132.0, 136.9, 137.9, 168.7, 174.5. ν_{max} (KBr): 3054, 2857, 1596, 1462, 1338, 1174, 902, 718, 691 cm^{-1}. $C_{23}H_{18}N_2OS$ (370.48): calcd C 74.57, H 4.90, N 7.56, S 8.65; found C 74.73, H 5.08, N 7.38, S 8.83.

4.6.13. N-(1-Hydroxy-10a,12a-dimethyl-7-phenyl-1,2,3,3a,3b,4,5,5a,6,7,10,10a,10b,11,12,12a-hexadecahydro-9-thia-7-aza-dicyclopenta[a,h]-phenanthren-8-ylidene)-benzamide (**1f**)

Dark red gummy liquid, R_f (25% EtOAc/hexane) 0.21. δ_H (400 MHz, $CDCl_3$): 0.76 (s, 3H), 0.86 (s, 3H), 0.80–2.00 (m, 19H), 2.31 (d, 1H, J=8 Hz), 2.60 (d, 1H, J=16 Hz), 3.65 (t, 1H, J=8.4 Hz), 4.15 (m, 1H), 7.42 (m, 7H), 7.81 (d, 1H, J=7.2 Hz), 8.03 (d, 2H, J=7.2 Hz). δ_C (100 MHz, $CDCl_3$): 11.2, 12.0, 21.0, 23.5, 28.5, 30.5, 31.2, 34.1, 35.7, 36.5, 36.7, 37.0, 37.8, 42.0, 43.0, 51.0, 53.8, 81.9, 117.2, 127.6, 128.0, 128.7, 129.1, 129.3, 129.4, 130.1, 131.3, 132.1, 137.2, 137.3, 168.6, 169.7, 174.2. ν_{max} (KBr): 3131, 2923, 2878, 1654, 1608, 1580, 1376, 1243, 1149, 764, 695 cm^{-1}. $C_{33}H_{38}N_2O_2S$ (526.75): calcd C 75.25, H 7.27, N 5.32, S 6.09; found C 75.41, H 7.36, N 5.26, S 6.18.

4.6.14. 3,4-Diphenyl-2-phenylimino-3H-thiazole (**7b**)

White needles, R_f (25% EtOAc/hexane) 0.69, mp 189–192 °C. δ_H (400 MHz, $CDCl_3$): 5.94 (s, 1H), 6.95–7.40 (m, 15H). δ_C (100 MHz, $CDCl_3$): 97.4, 121.8, 123.4, 127.7, 128.3, 128.4, 128.5, 129.0, 129.1, 129.6, 131.8, 138.1, 140.1, 152.1, 160.4. ν_{max} (KBr): 3049, 2923, 1618, 1577, 1486, 1360, 1138, 710, 694 cm^{-1}. $C_{21}H_{16}N_2S$ (328.44): calcd C 76.80, H 4.91, N 8.53, S 9.76; found C 76.68, H 5.04, N 8.62, S 9.58.

4.6.15. 4-Methyl-3,5-diphenyl-2-phenylimino-3H-thiazole (**7d**)

White crystalline solid, R_f (25% EtOAc/hexane) 0.74, mp 177–179 °C. δ_H (400 MHz, $CDCl_3$): 1.93 (s, 3H), 7.01 (m, 2H), 7.26 (m, 3H), 7.33 (m, 3H), 7.43 (m, 2H), 7.54 (m, 2H). δ_C (100 MHz, $CDCl_3$): 14.2, 109.6, 121.8, 123.2, 127.3, 128.7, 128.8, 129.2, 129.4, 129.7, 130.3, 132.8, 138.0, 152.2, 159.4. ν_{max} (KBr): 3021, 2854, 1618, 1577, 1489, 1352, 1141, 760, 688 cm^{-1}. $C_{22}H_{18}N_2S$ (342.47): calcd C 77.16, H 5.30, N 8.18, S 9.36; found C 77.23, H 5.26, N 8.31, S 9.24.

4.6.16. 10a,12a-Dimethyl-8-phenylimino-7-phenyl-l,2,3,3a,3b,4,5,5a,6,7,8,10,10a,10b,11,12,12a-hexadecahydro-1H-9-thia-7-aza-dicyclopenta[a,h]-phenanthren-1-ol (**7f**)

White amorphous solid, R_f (25% EtOAc/hexane) 0.25, mp 95–98 °C. δ_H (400 MHz, $CDCl_3$): 0.73 (s, 3H), 0.86 (s, 3H), 0.82–2.30 (m, 20H), 3.60 (t, 1H, J=8.8 Hz), 4.18 (m, 1H), 7.03 (m, 2H), 7.37 (m, 8H). δ_C (100 MHz, $CDCl_3$): 11.2, 12.0, 20.9, 23.5, 28.5, 28.9, 30.5, 31.2, 35.7, 36.7, 37.0, 38.2, 41.8, 42.9, 50.9, 53.8, 81.9, 106.3, 121.9, 123.2, 125.2, 126.8, 128.3, 128.8, 129.4, 129.5, 137.5, 152.2, 160.8. ν_{max} (KBr): 3133, 2928, 2886, 1609, 1577, 1378, 1149, 764, 695 cm^{-1}. *m/z*: 499 (M+1). $C_{32}H_{38}N_2OS$ (498.74): calcd C 77.07, H 7.68, N 5.62, S 6.43; found C 76.84, H 7.71, N 5.57, S 6.50.

4.6.17. 2-Benzoylimino-4,5-dihydro-1H-naphtho[1,2-d]-3-(p-tolyl)-thiazole (**3g**)

White cubes, R_f (25% EtOAc/hexane) 0.62, mp 196–197 °C. δ_H (400 MHz, $CDCl_3$): 2.49 (s, 3H), 2.81 (t, 2H, J=7.2 Hz), 3.03 (t, 2H, J=7.2 Hz), 6.35 (d, 1H, J=8 Hz), 6.88 (t, 1H, J=7.2 Hz), 7.09 (t, 1H, J=7.2 Hz), 7.23 (t, 2H, J=6.8 Hz), 7.36 (m, 6H), 8.11 (d, 2H, J=7.2 Hz). δ_C (100 MHz, $CDCl_3$): 21.6, 23.0, 30.0, 122.3, 123.2, 126.5, 126.6, 127.5, 128.0, 128.1, 128.5, 129.5, 130.0, 131.3, 131.5, 136.3, 136.4, 137.1, 139.0, 169.0, 174.5. ν_{max} (KBr): 3025, 3002, 2927, 2837, 1651, 1597, 1563, 1470, 1340, 1316, 1163, 905, 758, 714 cm^{-1}. $C_{25}H_{20}N_2OS$ (396.51): calcd C 75.73, H 5.08, N 7.06, S 8.09; found C 75.79, H 5.18, N 7.18, S 8.23.

4.6.18. 2-Benzoylimino-4,5-dihydro-7-methoxy-1H-naphtho[1,2-d]-3-(p-tolyl)-thiazole (**3h**)

White crystalline solid, R_f (25% EtOAc/hexane) 0.53, mp 197–199 °C. δ_H (400 MHz, $CDCl_3$): 2.50 (s, 3H), 2.80 (t, 2H, J=6.8 Hz), 3.02 (t, 2H, J=6.8 Hz), 3.74 (s, 3H), 6.25 (d, 1H, J=8.8 Hz), 6.41 (d, 1H, J=8.8 Hz), 6.79 (s, 1H), 7.34 (m, 7H), 8.09 (d, 2H, J=8.8 Hz). δ_C (100 MHz, $CDCl_3$): 21.6, 22.9, 30.2, 55.4, 111, 114.9, 124.6, 127.8, 128.1, 129.4, 129.7, 130.0, 131.5, 136.4, 137.1, 138.6, 139.0, 159.9, 168.9, 174.4. ν_{max} (KBr): 3021, 2924, 2841, 1649, 1602, 1563, 1468, 1339, 1318, 1268, 1165, 905, 756, 694 cm^{-1}. $C_{26}H_{22}N_2O_2S$ (426.54): calcd C 73.21, H 5.20, N 6.57, S 7.52; found C 73.14, H 5.09, N 7.58, S 7.67.

4.6.19. 5,5′-Bis-[2-benzoylimino-4-methyl-3-(p-tolyl)-3H-thiazole] (**3i**)

White amorphous solid, R_f (25% EtOAc/hexane) 0.65, mp 335–338 °C. δ_H (400 MHz, $CDCl_3$): 2.13 (s, 6H), 2.51 (s, 6H), 7.30 (m, 8H), 7.41 (m, 6H), 8.05 (d, 4H, J=8 Hz). δ_C (100 MHz, $CDCl_3$): 14.1, 21.6, 109.5, 127.9, 128.1, 129.6, 130.5, 131.8, 134.6, 135.1, 136.7, 139.7, 169.1, 174.9. ν_{max} (KBr): 3063, 2909, 1602, 1572, 1475, 1242, 818 cm^{-1}. *m/z*:

615 (M+1). $C_{36}H_{30}N_4O_2S_2$ (614.79): calcd C 70.33, H 4.92, N 9.11, S 10.43; found C 70.42, H 5.08, N 9.03, S 10.52.

*4.6.20. 2-Benzoylimino-4-methyl-3-(p-tolyl)-5-ethoxy carbonylcarboxylic acid ethyl ester-3H-thiazole (**3j**)*

White crystalline, R_f (25% EtOAc/hexane) 0.35, mp 165–167 °C. δ_H (400 MHz, $CDCl_3$): 1.36 (t, 3H, J=7.2 Hz), 2.40 (s, 3H), 2.48 (s, 3H), 4.32 (q, 2H, J=7.2 Hz), 7.28 (m, 7H), 8.00 (d, 2H, J=7.2 Hz). δ_C (100 MHz, $CDCl_3$): 14.2, 14.4, 21.5, 61.4, 127.8, 128.1, 129.1, 129.5, 130.5, 131.9, 134.2, 136.4, 139.8, 144.6, 162.2, 169.2, 175.2. ν_{max} (KBr): 3061, 2997, 2926, 1678, 1608, 1514, 1465, 1317, 1299, 1096, 909, 720 cm^{-1}. $C_{21}H_{20}N_2O_3S$ (380.47): calcd C 66.30, H 5.30, N 7.36, S 8.43; found C 66.28, H 5.18, N 7.28, S 8.38.

*4.6.21. 2-Benzoylimino-5-methyl-3-(p-tolyl)-3H-thiazole (**3k**)*

White needles, R_f (25% EtOAc/hexane) 0.52, mp 106–107 °C. δ_H (400 MHz, $CDCl_3$): 2.28 (s, 3H), 2.39 (s, 3H), 6.80 (s, 1H), 7.34 (m, 7H), 8.10 (d, 2H, J=8 Hz). δ_C (100 MHz, $CDCl_3$): 12.7, 21.2, 121.6, 122.7, 125.5, 127.9, 129.3, 129.6, 131.3, 136.0, 136.8, 138.2, 167.2, 174.0. ν_{max} (KBr): 3066, 2913, 1630, 1600, 1570, 1474, 1384, 1344, 1240, 902, 816, 703 cm^{-1}. $C_{18}H_{16}N_2OS$ (308.41): calcd C 70.10, H 5.23, N 9.08, S 10.40; found C 69.92, H 5.28, N 9.23, S 10.51.

*4.6.22. 3-Prop-2-ynyl-4,5,6,7-tetrahydro-3H-benzothiazol-2-ylideneamine (**13d**)*

Colourless liquid, R_f (55% EtOAc/hexane) 0.32. δ_H (400 MHz, $CDCl_3$): 0.81 (s, 4H), 1.52 (s, 2H), 1.61 (s, 2H), 2.12 (m, 1H), 3.56 (br s, 1H), 3.90 (s, 2H). δ_C (100 MHz, $CDCl_3$): 19.6, 20.5, 20.9, 21.0, 44.6, 73.7, 75.2, 113.8, 132.4, 165.6. ν_{max} (KBr): 3269, 3109, 2941, 2844, 2124, 1649, 1622, 1558, 1396, 1120, 1024, 900, 720, 707, 591 cm^{-1}. $C_{10}H_{12}N_2S$ (192.28): calcd C 62.47, H 6.29, N 14.57, S 16.68; found C 62.56, H 6.31, N 14.52, S 16.71.

*4.6.23. 3-Allyl-4,5,6,7-tetrahydro-3H-benzothiazol-2-ylideneamine (**13e**)*

Colourless liquid, R_f (55% EtOAc/hexane) 0.35. δ_H (400 MHz, $CDCl_3$): 1.78 (s, 4H), 2.30 (s, 4H), 3.60 (br s, 1H), 4.36 (d, 2H, J=2.8 Hz), 5.10 (d, 1H, J=17.2 Hz), 5.16 (d, 1H, J=10.4 Hz), 5.87 (m, 1H). δ_C (100 MHz, $CDCl_3$): 21.6, 22.4, 22.9, 23.0, 48.2, 116.6, 118.5, 129.3, 133.8, 166.9. ν_{max} (KBr): 3221, 3176, 3010, 1623, 1556, 1423, 688 cm^{-1}. $C_{10}H_{14}N_2S$ (194.30): calcd C 61.82, H 7.26, N 14.42, S 16.50; found C 61.87, H 7.19, N 14.51, S 16.46.

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