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Regioselective synthesis of new 2,5,6-trisubstituted 5,6-dihydro-2H-pyrazolo[3,4-d]thiazoles from 5-dimethylaminoethylene-thaozolidin-4-thiones

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Regioselective synthesis of new 2,5,6-trisubstituted 5,6-dihydro-2H-pyrazolo[3,4-d]thiazoles from 5-dimethylaminoethylene-thaozolidin-4-thiones

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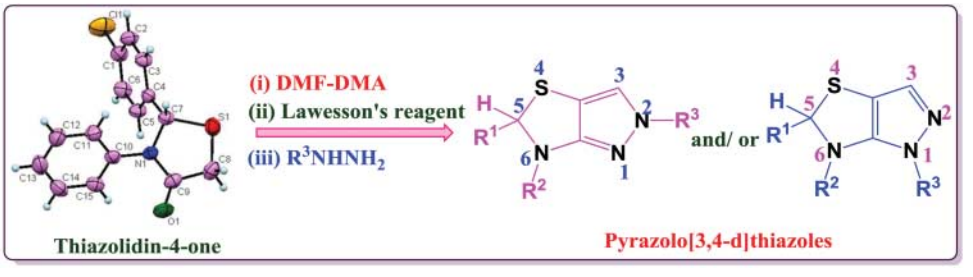
Thiazolidin-4-ones assembled through one-pot three-component (carbonyl compound, amine and ethyl mercaptoacetate) reactions in the presence of dicyclohexyl carbodiimide, on simultaneous treatment with dimethyl formamide dimethylacetal and Lawesson's reagent furnished 5-dimethylaminomethylene thiazolidin-4-thiones. These thiones on condensation with hydrazine derivatives afforded 2,5,6-trisubstituted-5,6-dihydro-2H-pyrazolo[3,4-d]thiazoles **4** and not their possible 1,5,6-trisubstituted regioisomers **5.** Results of single-crystal X-ray diffraction studies of thiazolidin-4-one **1b** have been reported. The structures of all the synthesized compounds were established by spectral data. DFT studies on regioisomers were carried out using B3LYP with the 6-31G** basis set and carbon NMR shifts of **4** show good correlation with experimental values.



Keywords: pyrazolo [3,4-d]thiazole; thiazolidin-4-one; Lawesson's reagent; DMF-DMA; thiazolidin-4-thione; spectral data; DFT

1. Introduction

Heterocyclic compounds have a wide variety of applications and represent about three-fourth of commercially available pharmaceuticals and agrochemicals. Pyrazoles and thiazoles are important classes of heterocycles possessing a wide variety of biological activities [1–3] and their utility as medicines is well established. During the last few decades the chemistry of fused bicyclic scaffolds has attracted remarkable attention due to their biological activities

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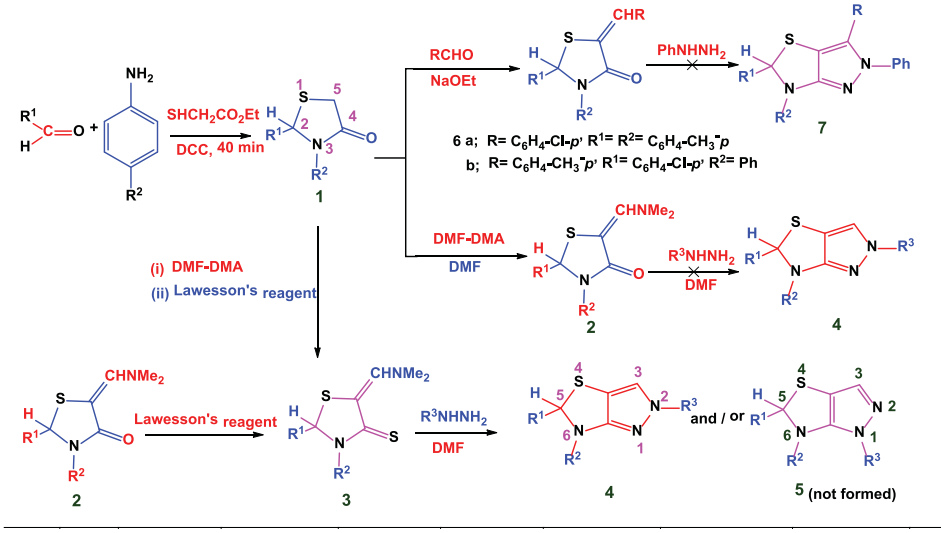
such as pyrazolopyridines as potential antihypertensive [4] and anti-inflammatory agents,[5] pyrazolopyrimidines as antiviral [6] and antitumor agents,[7] pyrazolo[5,1-c][1,2,4]triazines as cytotoxic agents,[8] thieno[2,3-e]indazole derivatives as IkB kinase inhibitors, [9] etc. This bioactive profile of bicyclic scaffolds prompted us to undertake the synthesis of pyrazolo[3,4-d]thiazole ring system. Despite a number of general methods available for pyrazole and thiazole derivatives, it is difficult to construct the bicyclic scaffolds with these moieties. Due to the lack of general synthetic methods only a few reports on the synthesis of pyrazolo[3,4-d]thiazole have appeared in the literature.[10–14] In continuation of our work on the synthesis of biologically active heterocycles,[15,16] we report herein an interesting route to the regioselective synthesis of 1,3,5-trisubstituted-5,6-dihydro-2H-pyrazolo[3,4-d]thiazoles starting with the reaction of enaminones of thiazolidin-4-ones with hydrazine derivatives.

2. Result and discussion

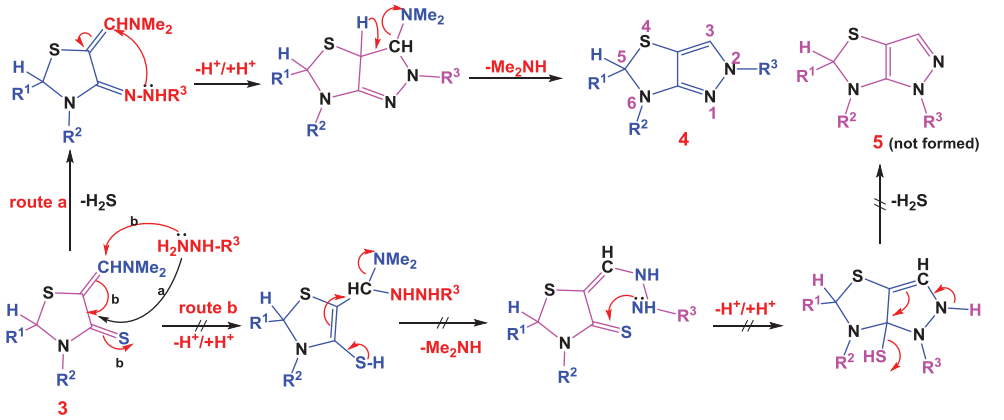
The synthesis of thiazolidin-4-ones **1** is described in the literature from carbonyl compounds, amines and mercaptoacetic acid using various dehydrating agents such as molecular sieves, anhyd. $ZnCl_2$,[17] sodium sulfate,[18] *N*,*N*-dicyclohexylcarbodiimide (DCC), [19] etc. Recently several publications have reported environment-friendly methods for their synthesis such as microwave irradiation,[20] ultrasonication [21] and the use of ionic liquids.[22,23] Herein, we have assembled thiazolidin-4-one rings in one-pot cyclocondensations of aldehydes, amines and ethyl mercaptoacetate in the presence of DCC in just 40 min in quantitative yields. The structure of this ring system is well established in the literature by spectral data. We report here single-crystal X-ray diffraction studies of 2-(4-chlorophenyl)-3-phenylthiazolidin-4-one **1b** in the crystallographic section. Thiazolidin-4-one **1** on treatment with *N*, *N*-dimethylformamide-dimethyl acetal (DMF-DMA) generated 5-dimethylaminomethylene derivatives **2**. Condensations of compound **2** with hydrazine derivatives was attempted to synthesize the pyrazolo[3,4-d]thiazole



4 /5	a	b	c	d	e	f	g	h	i
R^1	Ph	Ph	Ph	C_6H_4-Cl-*p*	C_6H_4-Cl-*p*	C_6H_4-Cl-*p*	C_6H_4-CH_3-*p*	C_6H_4-CH_3-*p*	C_6H_4-CH_3-*p*
R^2	Ph	Ph	Ph	Ph	Ph	Ph	C_6H_4-CH_3-*p*	C_6H_4-CH_3-*p*	C_6H_4-CH_3-*p*
R^3	Ph	C_6H_4-Cl-*p*	C_6H_4-CH_3-*o*	Ph	C_6H_4-Cl-*p*	C_6H_4-CH_3-*o*	Ph	C_6H_4-Cl-*p*	C_6H_4-CH_3-*o*

Scheme 1. Synthetic route to the synthesis of 5,6-dihydro-2H-pyrazolo[3,4-d]thiazoles.

system **4** (Scheme 1). Unfortunately, several attempts with acidic as well as basic reagents did not result in the ring closure reaction. In the literature, the synthesis of pyrazolo[3,4-d]thiazole ring system has been reported from condensation of 5-arylidene-4-thiazolidinones with hydrazine and its derivatives.[24,25] We also made several unsuccessful attempts to achieve the synthesis of pyrazolo[3,4-d]thiazole ring **7** from the reaction of 5-arylidene-4-thiazolidinones **6** with phenyl hydrazine under acidic as well as basic conditions. In a recent report,[26] 5-arylidene-4-thiazolidinones have been converted to more reactive thiazolidine-thione and then condensed with hydrazine derivatives to achieve the synthesis of pyrazolo[3,4-d]thiazoles. Based upon the same idea, 5-dimethylaminomethylene thiazolidin-4-one **2** was converted into thiazolidine-thione **3** by Lawesson's reagent according to the reported procedure [27] in anticipation that it would enhance the reactivity of the lactam function (Scheme 1). Compound **3** was also obtained in a single step on simultaneous treatment of thiazolidin-4-one **1** with DMF-DMA and Lawesson's reagent in toluene. Thiazolidine-thione **3** on condensation with hydrazine derivatives in DMF furnished a single product (TLC) **4** and not its possible regioisomer **5**. This cyclocondensation of **3** with hydrazine derivatives can possibly proceed via route a (via hydrazone formation) or b (Scheme 2) leading to the synthesis of **4** and **5**, respectively. There is no direct evidence to support route a mechanism in this case but several reports in the literature [25,26] have reported the condensation of hydrazine and its derivatives with 5-arylidene-thiazolidin-4-one or 5-arylidene-thiazolidine-4-thione through hydrazone formation (route a). Based upon these findings it is presumed that in the present case the reaction proceeds through route a mechanism and consequently isomer **4** is formed. We tried to obtain crystals of compounds **4a–i** in different solvents and we succeeded only for **4c**. Unfortunately, the crystals of **4c**, were of poor quality and did not show reflection even after a long exposure time to X-rays and as a consequence we could not obtain the crystal structure. Since the crystal structure of the product **4** is not available and to validate our claim for structure **4**, DFT studies on the regioisomers (**4a** and **5a**) were carried out using B3LYP with a 6-31G** basis set to give carbon NMR shifts that show good correlation with experimental results (computational studies section). The structure of compound **4** is also corroborated by additional analytical and spectral data. For example, the methine proton of the pyrazole ring in compound **4** appears between δ 8.44 and 8.68 in ^{1}H NMR spectra. The structures of **4a–i** are also supported by their molecular ion peaks $[M + H^+]$ in their mass spectra. Finally, the elemental analysis data of the synthesized compounds are in good agreement with calculated values (within the range of $\pm$0.4%).



Scheme 2. Plausible mechanism to the synthesis of 5,6-dihydro-2H- pyrazolo[3,4-d]thiazole ring.

2.1. *Crystallographic studies*

X-ray diffraction measurements were performed on X Calibur EOS OXFORD Diffractometer at 293 (2) K. The intensity data were collected using graphite monochromated Mo-Kα radiation ($\lambda = 0.71073$ Å). The structure was solved by a direct method using the SHELX-97 software package [28] and refined by full-matrix least-squares procedures on F^2. All non-hydrogen atoms were refined with anisotropic thermal parameters. The compound **1b** crystallizes in space group

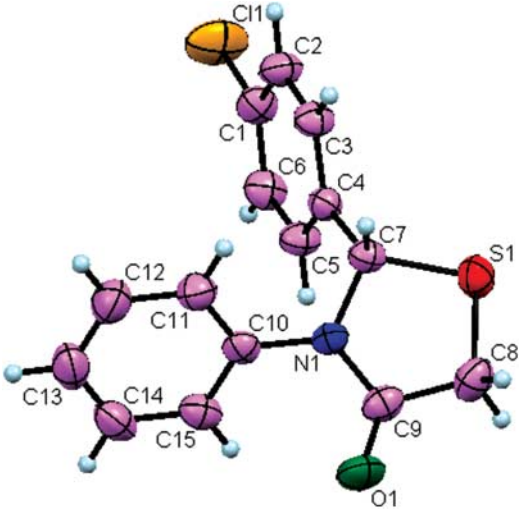


Figure 1. An ORTEP diagram of 2-(4-chlorophenyl)-3-phenylthiazolidin-4-one (**1b**) with non-hydrogen ellipsoids drawn at 50% probability level.

Table 1. Crystal data and structure refinement parameters of 2-(4-chlorophenyl)-3-phenylthiazolidin-4-one (**1b**).

CCDC no.	943547
Empirical formula	$C_{15}H_{12}ClNOS$
Formula weight	289.03
Temperature (K)	293 (2)
Wavelength (Å)	0.71073 Å
Space group	*P*-1
Unit cell dimensions	
a (Å)	9.7330 (4)
b (Å)	13.7316 (7)
c (Å)	10.3892 (5)
α (°)	90.00
β (°)	97.973 (4)
γ (°)	90.00
Volume (Å^3)	1375.09 (11)
Z	4
Density (calculated) (Mg/m^3)	1.255 Mg/m^3
Absorption coefficient (mm^{-1})	0.265 mm^{-1}
Theta range for data collection	3.07–29.27
Reflections collected	6310
Independent reflections	2308
Data/restraints/parameters	3158/0/173
Goodness of fit on F^2	1.067
Final *R* indices [$I > 2\sigma(I) = 2591$ data]	$R_1 = 0.0457$, $wR_2 = 0.0993$
R indices (all data)	$R_1 = 0.0698$, $wR_2 = 0.1134$
Largest diff. peak and hole (eÅ^{-3})	−0.457, 0.398

P-1 with $Z = 4$ and cell parameters $a = 9.7330\ (4)$ Å, $b = 13.7316\ (7)$ Å, $c = 10.3892\ (5)$ Å, $\alpha = 90.00°$, $\beta = 97.973(4)°$, $\gamma = 90.00°$. The ORTEP diagram obtained from the X-ray structure of **1b** is shown in Figure 1. The crystallographic data and refinement parameters of **1b** are reported in Table 1. CCDC 943547 contains the supplementary crystallographic data and these data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

2.2. *Computational studies*

The molecular geometry optimization and carbon NMR spectrum calculations were performed with the Jaguar software package version 7.6 by using DFT methods with B3LYP (Becke three parameter Lee–Yang–Parr) exchange correlation functional, which combines the hybrid exchange functional of Becke, with the gradient-correlation functional of Lee, Yang and Parr.[29] The 6-31G** basis set was used for gas phase calculations of the regioisomeric structures **4a** and **5a**. These calculations compensate for the lack of X-ray structures for **4a** or **5a**. The optimized **4a** and **5a** structures with atom numbering schemes are shown in Figures 2 and 3.

Shielding tensors for structures **4a** and **5a** were evaluated by using B3LYP functional with the basis set given above. In order to express the chemical shifts in ppm, the geometry of tetramethylsilane (TMS) and chloroform molecules were optimized and then the carbon NMR

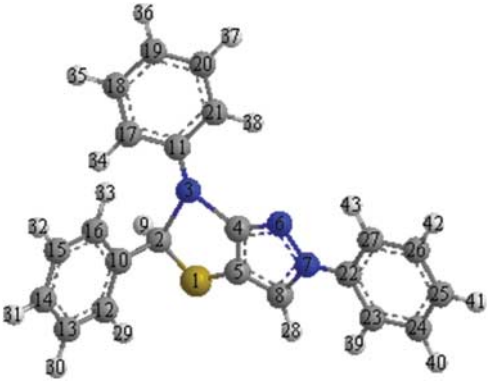


Figure 2. Optimized structure of **4a**.

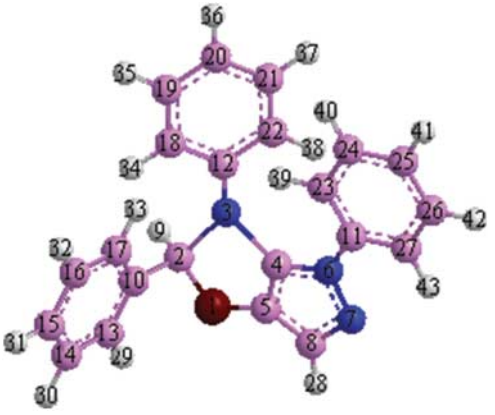


Figure 3. Optimized structure of **5a**.

spectra were calculated. Using the ^{13}C NMR shielding of TMS of δ 202.8593 the calculated isotropic shielding constants σ_i were then transformed to chemical shifts relative to TMS by the equation $\delta_i = \sigma_{TMS} - \sigma_i$.

A comparison of experimental and calculated ^{13}C NMR chemical shifts (ppm) of compounds **4a** and **5a** is reported in Table 2. Since field effects are prominent in carbon NMR, it is found that correlation between theoretical and experimental ^{13}C NMR of isomer **4a** is 0.9506 and isomer **5a** is 0.9113 (Figure 4). The correlation is good for structure **4a** and not for isomer **5a**. Frequency calculations of optimized structures **4a** and **5a** did not show any negative frequency and this verifies that there are no stationary points. The *Z*-matrix (*X*, *Y*, *Z* coordinates of minimized structures **4a** and **5a**) are reported as supplementary information (Tables S1 and S2, http://dx.doi.org/10.1080/17415993.2014.944912). Zero point energies of **4a** and **5a** are 214.64 and 215.53 kcal/mol, respectively. This shows that compound **4a** is more stable than isomer **5a**.

Table 2. Experimental and calculated ^{13}C NMR chemical shifts (ppm) of compound **4a** and isomer **5a**.

	Compound **4a**			Compound **5a**		
Entry	Expt. NMR	Calc. Shield	Calc. NMR	Entry	Calc. Shield	Calc. NMR
C2	63.92	134.5292	71.41	C2	125.6302	80.71
C4	163.72	45.2233	164.75	C4	55.0144	154.52
C5	122.20	97.8303	109.77	C5	98.2488	109.33
C8	137.29	78.7371	129.72	C8	68.071	140.87
C10	152.14	59.0237	150.33	C10	57.2478	152.18

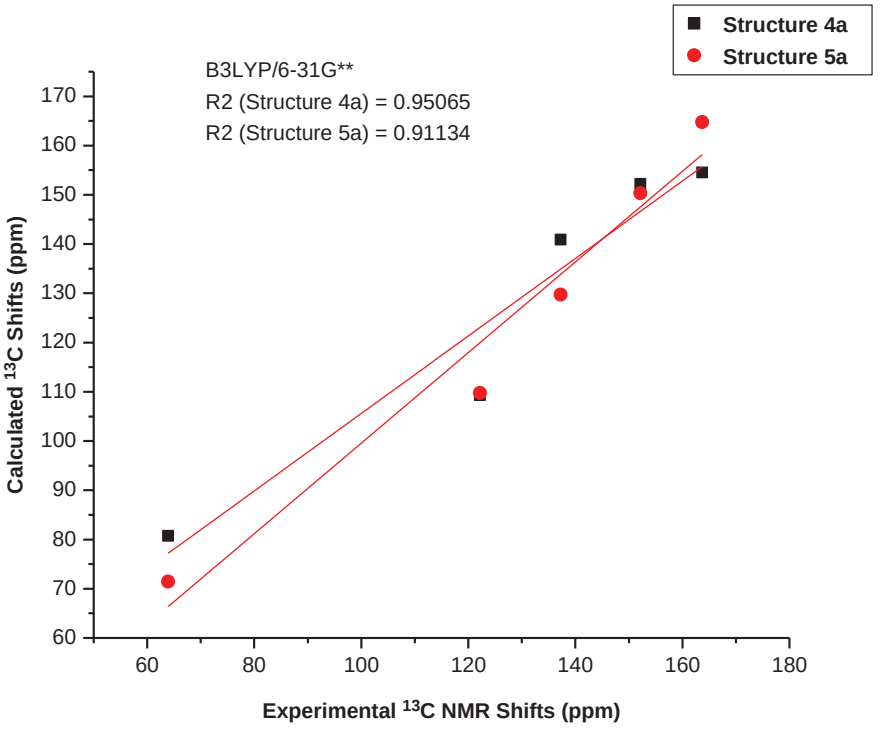


Figure 4. Plot of the calculated vs. experimental ^{13}C NMR chemical shifts (ppm) of **4a** and **5a**.

3. Experimental

3.1. *Instrumentations*

Melting points were determined in sulfuric acid bath and are reported uncorrected. TLC was performed on silica gel G plates using pet ether–ethyl acetate (4:1) as eluent and iodine vapors as visualizing agent. IR spectra were recorded on an ABB FTIR spectrometer and the results are reported in cm^{-1}. ^1H NMR and ^{13}C NMR were recorded in $CDCl_3$ and DMSO-d_6 on a BRUKER ADVANCE II 400 NMR spectrometer using TMS as an internal standard (chemical shift in δ, ppm). Mass spectra were recorded on a WATERS, Q-TOF MICROMASS (LC-MS) instrument. The elemental analyses of the compounds were performed on Euro EA 3000 Elemental Analyzer. X-ray diffraction was performed on X Calibur EOS OXFORD Diffractometer.

3.2. *General procedure for the synthesis of 1a–c*

Compounds **1a–c** were synthesized by slight modification (using ethyl mercapto acetate in place of mercapto acetic acid) in the reported procedure.[19] To an ice cold solution of an aldehyde (1.0 mmol) and an amine (2.0 mmol) in THF (15 mL), ethyl mercaptoacetate (2.5 mmol) was added. After 5 min DCC (1.5 mmol) was added to the reaction mixture and the mixture was stirred for 40 min at room temperature. N,N'-dicyclohexylurea was then removed by filtration and THF was removed completely under reduced pressure. The residue was extracted with ethyl acetate and organic layer was washed successively with (5%) aq. citric acid, (5%) aq. sodium bicarbonate and finally with brine. The organic layer was dried over anhyd. sodium sulfate and solvent was removed under reduced pressure. The crude solid obtained was recrystallized from ethyl acetate.

3.2.1. *2,3-Diphenylthiazolidin-4-one (**1a**)*

White solid, yield 85%, mp 128–130°C, lit. [22] mp 131–132°C.

3.2.2. *2-(4-Chlorophenyl)-3-phenylthiazolidn-4-one (**1b**)*

White crystalline solid, yield 87%, mp 124–126°C, lit. [19] mp 124–127°C.

3.2.3. *2,3-Di-p-tolylthiazolidin-4-one (**1c**)*

White solid, yield 86%, mp 112–114°C, lit. [22] mp 119–120°C.

3.3. *General procedure for the synthesis of 2(a–c)*

A mixture of thiazolidin-4-one **1** (1.0 mmol) and DMF-DMA (10 mmol) in DMF (5.0 mL) was refluxed for 50 min. The reaction mixture was then cooled and extracted with ethyl acetate (2 × 25 mL). The organic layer was washed with brine solution and dried over anhydrous Na_2SO_4. The excess ethyl acetate was then removed under reduced pressure and the solid obtained was filtered and recrystallized from ethanol.

3.3.1. *5-[(Dimethylamino)methylene]-2,3-diphenylthiazolidin-4-one (**2a**)*

White crystalline solid, yield 85%, mp 198–200°C. IR (cm^{-1}): 1697 (C=O), 1490 (C=C); ^1H NMR (400 MHz, DMSO-d_6): δ 3.02 (s, 6H, NMe_2), 6.40 (s, 1H, H-2), 7.03–7.07 (t, 1H, C_6H_5, $J = 7.32$ Hz), 7.19–7.28 (m, 6H, C_6H_5), 7.31–7.33 (m, 4H, C_6H_5 and =CH). Anal. Calcd for $C_{18}H_{18}N_2OS$: C, 69.65; H, 5.84; N, 9.02; S, 10.33; found: C, 69.86%; H, 5.95%; N, 9.14%; S, 10.48%.

3.3.2. *2-(4-Chlorophenyl)-5-[(dimethylamino)methylene]-3-phenylthiazolidin-4-one (**2b**)*

Yellow solid, yield 90%, mp 166–168°C. IR (cm^{-1}): 1705 (C=O), 1495 (C=C); ^1H NMR (400 MHz, $CDCl_3$): δ 3.03 (s, 6H, NMe_2), 6.10 (s, 1H, H-2), 7.10 (m, 1H, C_6H_5), 7.20–7.27 (m, 8H, C_6H_5), 7.34 (s, 1H, =CH); mass m/z 345 ($M + H^+$, 100%). Anal. Calcd for $C_{18}H_{17}ClN_2OS$: C, 62.69; H, 4.97; N, 8.12; S, 9.30; found: C, 62.86%; H, 5.04%; N, 8.32%; S, 9.48%.

3.3.3. *5-[(Dimethylamino)methylene]-2,3-di-p-tolylthiazolidin-4-one (**2c**)*

White solid, yield 90%, mp 148–150°C. IR (cm^{-1}): 1695 (C=O), 1485 (C=C); ^1H NMR (400 MHz, DMSO-d_6): δ 2.22 (s, 3H, CH_3), 2.25 (s, 3H, CH_3), 3.00 (s, 6H, NMe_2), 6.33 (s, 1H, H-2), 7.01–7.06 (m, 4H, C_6H_5), 7.16–7.20 (m, 5H, C_6H_5 and =CH). Anal. Calcd for $C_{20}H_{22}N_2OS$: C, 70.97; H, 6.55; N, 8.28; S, 9.47; found: C, 70.82%; H, 6.68%; N, 8.42%; S, 9.62%.

3.4. *General procedure for the synthesis of 3(a–c)*

(a) A mixture of **2** (1.0 mmol) and Lawesson's reagent (1.0 mmol) in dry toluene (20 mL) was refluxed for 2 h. The solvent was removed under reduced pressure. The solid obtained on cooling was recrystallized from ethanol–DMF (3:1) mixture.

(b) A mixture of **1** (1.0 mmol) and DMF-DMA (1.5 mmol) in dry toluene was heated under reflux for 1–2 h (progress of the reaction was monitored by TLC). After completion of the reaction, Lawesson's reagent (1.0 mmol) was added to the reaction mixture and continued refluxing for 2 h. Toluene was removed completely under reduced pressure. The semisolid material obtained was extracted with ethyl acetate (2×15 mL). The extract was washed with brine (5%) solution and dried over anhydrous Na_2SO_4. The solid obtained on removal of solvent was crystallized from DMF-ethanol (1:3) mixture.

3.4.1. *5-[(Dimethylamino)methylene]-2,3-diphenylthiazolidine-4-thione (**3a**)*

Light brown solid, yield 65%, mp 108–110°C. IR (cm^{-1}): 1252 (C=S), 1490 (C=C); ^1H NMR (400 MHz, DMSO-d_6): δ 3.00 (s, 6H, NMe_2), 6.47 (s, 1H, H-2), 7.05–7.06 (t, 1H, C_6H_5, $J = 7.36$ Hz), 7.20–7.28 (m, 6H, C_6H_5), 7.31–7.35 (m, 4H, C_6H_5 and =CH); Mass m/z 327.1($M + H^+$, 100%); Anal. Calcd. For: $C_{18}H_{18}N_2S_2$: C, 66.22; H, 5.56; N, 8.58; S, 19.64; found: C, 66.46%; H, 5.64%; N, 8.72%; S, 19.48%.

3.4.2. *2-(4-Chlorophenyl)-5-[(dimethylamino)methylene]-3-phenylthiazolidine-4-thione (**3b**)*

Light brown solid, yield 65%, mp 120–122°C. IR (cm^{-1}): 1240 (C=S), 1490 (C=C); ^1H NMR (400 MHz, DMSO-d_6): δ 3.00 (s, 6H, NMe_2), 6.55 (s, 1H, H-2), 7.06 (m, 1H, C_6H_5), 7.23–7.27

(m, 3H, C_6H_5), 7.30–7.35 (m, 6H, C_6H_5 and =CH); Anal. Calcd. For: $C_{18}H_{17}ClN_2S_2$: C, 59.90; H, 4.75; N, 7.76%; S, 17.77%; found: C, 60.01%; H, 4.94%; N, 7.92%; S, 17.98%.

3.4.3. *5-[(Dimethylamino)methylene]-2,3-di-p-tolylthiazolidine-4-thione (**3c**)*

Brown solid, yield 65%, mp 158–60°C. IR (cm^{-1}): 1210 (C=S), 1490 (C=C); ^1H NMR (400 MHz, DMSO-d_6): δ 2.21 (s, 3H, CH_3), 2.23 (s, 3H, CH_3), 2.99 (s, 6H, NMe_2), 6.38 (s, 1H, H-2), 7.01–7.06 (m, 4H, C_6H_5), 7.17–7.19 (m, 5H, C_6H_5 and =CH); Anal. Calcd. for: $C_{20}H_{22}N_2S_2$: C, 67.76; H, 6.25; N, 7.90; S, 18.09; found: C, 67.92%; H, 6.40%; N, 8.03%; S, 18.28%.

3.5. *General procedure for the synthesis of 4(a–i)*

A solution of phenyl hydrazine hydrochloride (0.75 mmol), in ethanol (25 mL) was added while stirring to a solution of compound **3** (0.5 mmol) in DMF (5.0 mL). The reaction mixture was refluxed for 10–12 h. Evolution of hydrogen sulfide gas continues for 5–6 h. The progress of reaction was monitored by TLC. The reaction mixture was then cooled to room temperature and poured into ice cold water and separated solid was filtered, dried and recrystallized from ethanol.

3.5.1. *2,5,6-Triphenyl-5,6-dihydro-2H-pyrazolo[3,4-d]thiazole (**4a**)*

Orange solid, yield 40%, mp 188–190°C. IR (cm^{-1}): 1659 (C=N), 1489 (C=C); ^1H NMR (400 MHz, DMSO-d_6): δ 6.80 (s, 1H, H-5), 7.18–7.22 (m, 1H, C_6H_5), 7.25–7.31 (m, 5H, C_6H_5), 7.38–7.41 (m, 2H, C_6H_5), 7.46–7.52 (m, 5H, C_6H_5), 7.78–7.81 (m, 2H, C_6H_5), 8.47 (s, 1H, =CH of pyrazole ring); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 163.7, 152.1, 137.2, 137.1, 136.7, 131.3, 129.1, 128.7, 128.6, 127.0, 126.8, 125.3, 122.2, 63.9; mass m/z 356.1 ($M + H^+$, 90%). Anal. Calcd for $C_{22}H_{17}N_3S$: C, 74.34; H, 4.82; N, 11.82; S, 9.02; found: C, 74.42%; H, 5.01%; N, 11.96%; S, 9.18%.

3.5.2. *2-(4-Chlorophenyl)-5,6-diphenyl-5,6-dihydro-2H-pyrazolo[3,4-d]thiazole (**4b**)*

Yellow solid, yield 44%, mp 138–140°C. IR (cm^{-1}): 1645 (C=N), 1485 (C=C); ^1H NMR (400 MHz, DMSO-d_6): δ 6.88 (s, 1H, H-5), 7.18–7.22 (m, 1H, C_6H_5), 7.25–7.36 (m, 5H, C_6H_5), 7.39–7.42 (m, 2H, C_6H_5), 7.48–7.51 (dd, 2H, C_6H_5, $J = 1.16$ Hz, $J = 7.56$ Hz), 7.55–7.58 (m, 2H, C_6H_5), 7.79–7.81 (dd, 2H, C_6H_5, $J = 2.0$ Hz, $J = 4.8$ Hz), 8.48 (s, 1H, =CH of pyrazole ring); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 163.5, 150.6, 137.2, 137.0, 136.7, 136.2, 135.0, 129.5, 128.9, 128.8, 128.7, 127.1, 126.9, 125.4, 123.7, 63.9; mass m/z 390.2 ($M + H^+$, 35%). Anal. Calcd for $C_{22}H_{16}ClN_3S$: C, 67.77; H, 4.14; N, 10.78; S, 8.22; found: C, 67.52%; H, 4.31%; N, 10.87%; S, 8.38%.

3.5.3. *5,6-Diphenyl-2-(o-tolyl)-5,6-dihydro-2H-pyrazolo[3,4-d]thiazole (**4c**)*

Red needles, yield 42%, mp 188–190°C. IR (cm^{-1}): 1656 (C=N), 1484 (C=C); ^1H NMR (400 MHz, DMSO-d_6): δ 2.60 (s, 3H, CH_3), 6.83 (s, 1H, H-5), 7.19–7.23 (t, 1H, C_6H_5, $J =$ 7.52 Hz), 7.24–7.28 (m, 4H, C_6H_5), 7.30–7.35 (m, 2H, C_6H_5), 7.37–7.39 (m, 4H, C_6H_5), 7.46–7.48 (d, 2H, C_6H_5, $J = 7.56$ Hz), 7.58–7.60 (d, 1H, C_6H_5, $J = 8.0$ Hz), 8.68 (s, 1H, =CH of pyrazole ring); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 163.8, 150.7, 137.7, 137.3, 136.8, 131.3, 128.8, 128.7, 127.1, 126.8, 125.4, 114.8, 63.9, 18.3; mass m/z 370.1 ($M + H^+$, 100%); Anal.

Calcd for $C_{23}H_{19}N_3S$: C, 74.77; H, 5.18; N, 11.37; S, 8.68; found: C, 74.89%; H, 5.31%; N, 11.51%; S, 8.82%.

3.5.4. *5-(4-Chlorophenyl)-2,6-diphenyl-5,6-dihydro-2H-pyrazolo[3,4-d]thiazole (**4d**)*

Orange solid, yield 48%, mp 156–158°C. IR (cm^{-1}): 1652 (C=N), 1481 (C=C); ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.23 (s, 1H, H-5), 7.23–7.28 (m, 6H, C_6H_5), 7.32–7.36 (t, 2H, C_6H_5, $J = 7.48$), 7.45–7.48 (m, 3H, C_6H_5), 7.83–7.86 (m, 2H, C_6H_5), 8.65 (s, 1H, =CH of pyrazole ring); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 163.5, 150.6, 137.2, 137.0, 136.7, 136.2, 135.0, 129.5, 128.9, 128.8, 128.7, 127.1, 126.9, 125.4, 123.7, 63.9; mass m/z 390.1 ($M + H^+$, 21%). Anal. Calcd for $C_{22}H_{16}ClN_3S$: C, 67.77; H, 4.14; N, 10.78; S, 8.22; found: C, 67.42%; H, 4.31%; N, 11.01%; S, 8.38%.

3.5.5. *2,5-bis(4-chlorophenyl)-6-phenyl-5,6-dihydro-2H-pyrazolo[3,4-d]thiazole (**4e**)*

Orange solid, yield 52%, mp 160–162°C. IR (cm^{-1}): 1654 (C=N), 1481 (C=C); ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.87 (s, 1H, H-5), 7.19–7.23 (t, 1H, C_6H_5, $J = 7.40$ Hz), 7.31–7.37 (m, 4H, C_6H_5), 7.43–7.49 (m, 4H, C_6H_5), 7.53–7.56 (m, 2H, C_6H_5), 7.78–7.82 (m, 2H, C_6H_5), 8.49 (s, 1H, =CH of pyrazole ring); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 163.4, 150.6, 137.1, 136.5, 136.3, 136.1, 134.5, 133.7, 129.4, 129.0, 128.8, 128.7, 127.0, 125.4, 123.7, 63.1; mass m/z 424.1 ($M + H^+$, 30%). Anal. Calcd for $C_{22}H_{15}Cl_2N_3S$: C, 62.27; H, 3.56; N, 9.90; S, 7.56; found: C, 62.42%; H, 3.71%; N, 10.08%; S, 7.68%.

3.5.6. *5-(4-Chlorophenyl)-6-phenyl-2-(o-tolyl)-5,6-dihydro-2H-pyrazolo[3,4-d]thiazole (**4f**)*

Orange solid, yield 41%, mp 152–154°C. IR (cm^{-1}): 1649 (C=N), 1480 (C=C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.41 (s, 3H, CH_3), 6.22 (s, 1H, H-5), 7.22–7.34 (m, 11H, C_6H_5), 7.74–7.76 (d, 2H, C_6H_5, $J = 8.32$ Hz), 8.60 (s, 1H, =CH of pyrazole ring); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.4, 150.6, 137.1, 136.5, 136.3, 136.1, 134.5, 133.7, 129.4, 129.0, 128.8, 128.7, 127.0, 125.4, 123.7, 63.1; mass m/z 404.1 ($M + H^+$, 15%). Anal. Calcd for $C_{23}H_{18}ClN_3S$: C, 68.39; H, 4.49; N, 10.40; S, 7.94; found: C, 68.52%; H, 4.71%; N, 10.61%; S, 8.08%.

3.5.7. *2-Phenyl-5,6-di-p-tolyl-5,6-dihydro-2H-pyrazolo[3,4-d]thiazole (**4g**)*

Orange solid, yield 40%, mp 128–130°C. IR (cm^{-1}): 1652 (C=N), 1485 (C=C); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.22 (s, 6H, $2CH_3$), 6.74 (s, 1H, H-5), 7.04–7.11 (m, 4H, C_6H_5), 7.21–7.23 (m, 2H, C_6H_5), 7.27–7.32 (m, 2H, C_6H_5), 7.34–7.38 (m, 1H, C_6H_5), 7.43–7.47 (m, 2H, C_6H_5), 7.77–7.80 (m, 2H, C_6H_5), 8.44 (s, 1H, =CH of pyrazole ring); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 163.5, 152.1, 138.3, 136.9, 136.3, 134.3, 134.1, 131.4, 129.3, 129.2, 127.0, 125.3, 122.2, 63.8, 20.7, 20.5; mass m/z 384.1 ($M + H^+$, 52%). Anal. Calcd for $C_{24}H_{21}N_3S$: C, 75.16; H, 5.52; N, 10.96; S, 8.36; found: C, 75.32%; H, 5.71%; N, 11.12%; S, 8.48%.

3.5.8. *2-(4-Chlorophenyl)-5,6-di-p-tolyl-5,6-dihydro-2H-pyrazolo[3,4-d]thiazole (**4h**)*

Brown solid, yield 46%, mp 134–136°C. IR (cm^{-1}): 1654 (C=N), 1490 (C=C); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.25 (s, 6H, $2CH_3$), 6.79 (s, 1H, H-5), 7.05–7.10 (m, 2H, C_6H_5), 7.12–7.16 (m, 2H, C_6H_5), 7.25–7.32 (m, 2H, C_6H_5), 7.34–7.38 (m, 2H, C_6H_5), 7.40–7.48 (m, 2H, C_6H_5), 7.59–7.65 (m, 2H, C_6H_5), 8.44 (s, 1H, =CH of pyrazole ring); ^{13}C NMR (100 MHz,

DMSO-d_6) δ: 163.6, 152.3, 138.5, 136.9, 136.5, 134.5, 134.1, 131.5, 129.4, 129.3, 127.1, 125.4, 122.3, 63.9, 20.8, 20.6; mass m/z 418.1 ($M + H^+$, 10%). Anal. Calcd for $C_{24}H_{20}ClN_3S$: C, 68.97; H, 4.82; N, 10.05; S, 7.67; found: C, 69.18%; H, 4.71%; N, 10.21%; S, 7.48%.

3.5.9. *2-(o-tolyl)-5,6-di-p-tolyl-5,6-dihydro-2H-pyrazolo[3,4-d]thiazole (**4i**)*

Orange solid, yield 40%, mp 158–160°C. IR (cm^{-1}): 1656 (C=N), 1484 (C=C); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.22 (s, 3H, CH_3), 2.24 (s, 3H, CH_3), 2.59 (s, 3H, CH_3), 6.74 (s, 1H, H-5), 7.07–7.09 (d, 2H, C_6H_5, $J = 8.0$ Hz), 7.11–7.13 (d, 2H, C_6H_5, $J = 8.32$ Hz), 7.23–7.28 (m, 3H, C_6H_5), 7.31–7.33 (d, 2H, C_6H_5, $J = 8.36$ Hz), 7.38–7.39 (d, 2H, C_6H_5, $J = 4.04$ Hz), 7.57–7.59 (d, 1H, C_6H_5, $J = 8.0$ Hz), 8.66 (s, 1H, =CH of pyrazole ring); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 163.5, 152.4, 138.6, 136.4, 136.3, 134.5, 134.2, 131.6, 129.5, 129.2, 127.2, 125.5, 122.4, 63.8, 20.9, 20.5, 20.1; mass m/z 398.1 ($M + H^+$, 40%). Anal. Calcd for $C_{25}H_{23}N_3S$: C, 75.53; H, 5.83; N, 10.57; S, 8.07; found: C, 75.68%; H, 5.91%; N, 10.71%; S, 8.18%.

3.6. *General procedure for the synthesis of 6*

A mixture of compound **1** (0.5 mmol), aromatic aldehyde (0.5 mmol) and sodium ethoxide (0.02 g of sodium in 2.0 mL of absolute ethanol) in dry benzene (20 mL) was heated under reflux for 10–12 h. The progress of reaction was monitored by TLC. After completion, the reaction mixture was cooled and poured into ice cold water. The organic layer was separated and dried over fused calcium chloride. The solvent was removed under reduced pressure. The solid obtained was recrystallized from ethanol.

3.6.1. *(E)-5-(4-chlorobenzylidene)-2,3-di-p-tolylthiazolidin-4-one (**6a**)*

Yellow solid, yield 75%, mp 188–190°C. IR (cm^{-1}): 1696 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.22 (s, 3H, CH_3), 2.23 (s, 3H, CH_3), 6.82 (s, 1H, H-5), 7.09–7.15 (m, 4H, C_6H_5), 7.25–7.27 (d, 2H, C_6H_5, $J = 8.12$ Hz), 7.31–7.33 (d, 2H, C_6H_5, $J = 8.36$ Hz), 7.52–7.54 (t, 3H, C_6H_5, $J = 6.0$ Hz), 7.58–7.60 (t, 2H, C_6H_5 and =CH, $J = 2.04$ Hz). Anal. Calcd for $C_{24}H_{20}ClNOS$: C, 71.01; H, 4.97; N, 3.45; S, 7.90; found: C, 71.22%; H, 5.12%; N, 3.58%; S, 8.07%.

3.6.2. *(E)-2-(4-chlorophenyl)-5-(4-methylbenzylidene)-3-phenylthiazolidin-4-one (**6b**)*

Yellow solid, yield 72%, mp 170–172°C. IR (cm^{-1}): 1698 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.36 (s, 3H, CH_3), 6.71 (s, 1H, H-5), 7.17–7.21 (t, 1H, C_6H_5, $J = 7.36$ Hz), 7.24–7.43 (m, 12H, C_6H_5), 7.52 (s, 1H, =CH); Anal. Calcd for $C_{23}H_{18}ClNOS$: C, 70.49; H, 4.63; N, 3.57; S, 8.18; found: C, 70.61%; H, 4.87%; N, 3.69%; S, 8.31%.

3.7. *Attempted synthesis of 7*

A mixture of **6** (0.5 mmol), phenyl hydrazine (0.75 mmol) and anhydrous sodium acetate (1.0 mmol) in absolute ethanol (15 mL) was heated under reflux for 24–30 h. The progress of the reaction was monitored by TLC. Unfortunately, the reaction did not happen after 30 h and starting material was obtained. The reaction was attempted under acidic conditions (acetic acid) and basic conditions (piperidine). The starting material was obtained in all above cases.

Supplemental data

Supplemental data for this article can be accessed at 10.1080/17415993.2014.944912.

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