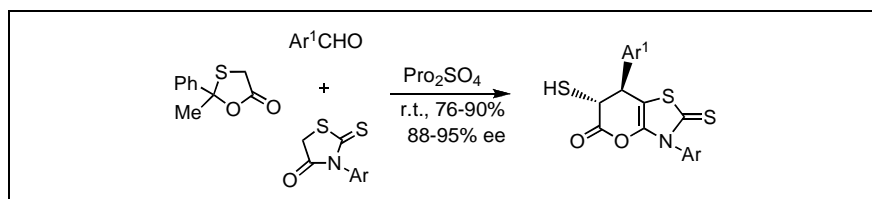


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A low hazardous, one-pot, expeditious annulation involving tandem Knoevenagel, Michael and ring transformation reactions of 3-arylrhodanines, aromatic aldehydes and a mercaptoacetyl transfer agent, 2-methyl-2-phenyl-1,3-oxathiolan-5-one, diastereoselectively yields 6-mercaptopyranothiazoles. The annulation is performed using a chiral ionic liquid (Pro_2SO_4) as the reaction medium and catalyst, and proceeds *via* an isolable intermediate.

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INTRODUCTION

In the present dynamic millenium, the discovery of novel multicomponent reactions (MCRs) has become an increasingly active area of research, yielding novel chemical scaffolds and combinatorial libraries in drug discovery efforts [1-5] as it offers significant advantages over conventional linear type syntheses [6-10]. Ionic liquids (ILs) have attracted increasing interest in the context of green chemistry owing to their great potential as environmentally benign reaction media [11-14], catalysts [14-16] and reagents [17,18]. A recent review [19] presents studies on the applications of chiral ionic liquids (CILs) not only as an opportunity but also a challenge for researchers. The chiral ionic liquid L-prolinium sulfate (Pro_2SO_4), which we have used in the present study, is directly obtainable from a natural α -amino acid [20].

Various pyran-2-one derivatives act as nonpeptidic HIV protease inhibitors [21], anticancer agents [22] and potent PPAR γ activator [23]. Thiazoles have been reported to exhibit a wide range of applications in drug development against inflammation [24], bacterial [25], and HIV infections [26]. Literature records that incorporation of a thiol function in heterocycles imparts interesting biological and therapeutic properties [27-34]. Thus, hitherto unreported target mercaptopyranothiazoles are expected to possess high pharmacological potential and could be attractive scaffolds for exploiting chemical diversity and generating a drug-like library to screen for lead candidates. Notably, neither known synthetic approaches to heterocycles nor functionalization reactions of heterocycles can be used for their synthesis.

As part of our ongoing research programme and continued interest in devising new solvent-free cyclization processes [35-39], we had to develop an efficient synthetic approach to pyranothiazoles incorporating a thiol function at C-6. For this purpose, we utilized the mercaptoacetyl transfer agent, 2-methyl-2-phenyl-1,3-

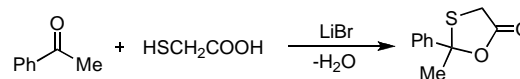


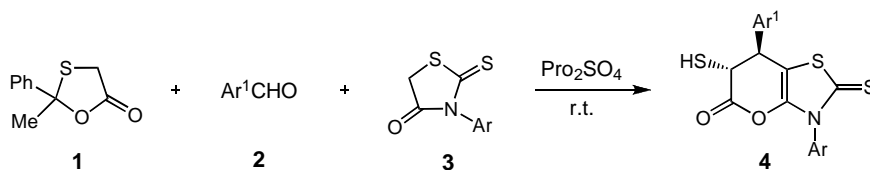
Figure 1 Formation of mercaptoacetyl transfer agent.

oxathiolan-5-one (Figure 1) [38], which leads to the desired mercaptoacetyllative heteroannulation and is the key element in the present successful synthetic strategy for the target compounds **4** (Scheme 1). It is noteworthy that acetophenone, which is used to activate mercaptoacetic acid to act as an efficient mercaptoacetyllative transfer agent, is automatically removed during the reactions yielding the compounds **4**. Furthermore, we used a chiral ionic liquid, L-prolinium sulfate (Pro_2SO_4), as the reaction medium and catalyst to achieve our goal expeditiously with high diastereoselectivity and enantiomeric excess (ee).

RESULTS AND DISCUSSION

The envisaged MCR was successful by stirring a mixture of 2-methyl-2-phenyl-1,3-oxathiolan-5-one (**1**), aromatic aldehydes (**2**), 3-arylrhodanines (**3**) and Pro_2SO_4 in THF at room temperature for 25-30 h. Isolation and purification by column chromatography afforded pyranothiazoles as a single diastereomer **4** in 76-90% yields

Scheme 1



Compd	Ar	Ar ¹	Time (h) ^a	Yield (%) ^{b,c}	(ee) ^d
4a	Ph	Ph	27	79	91
4b	Ph	4-ClC ₆ H ₄	25	90	88
4c	Ph	4-MeOC ₆ H ₄	25	87	88
4d	2-MeOC ₆ H ₄	Ph	30	88	93
4e	2-MeOC ₆ H ₄	4-ClC ₆ H ₄	29	85	92
4f	2-MeOC ₆ H ₄	4-MeOC ₆ H ₄	28	76	95
4g	4-MeOC ₆ H ₄	Ph	26	84	89
4h	4-MeOC ₆ H ₄	4-ClC ₆ H ₄	30	78	90
4i	4-MeOC ₆ H ₄	4-MeOC ₆ H ₄	27	77	92
4j	2-MeC ₆ H ₄	Ph	25	82	91
4k	2-MeC ₆ H ₄	4-ClC ₆ H ₄	28	90	94
4l	2-MeC ₆ H ₄	4-MeOC ₆ H ₄	28	85	93

^aStirring time at room temperature. ^bYield of isolated and purified products. ^cAll compounds gave C, H and N analyses within $\pm 0.36\%$ and satisfactory spectral (IR, ¹H NMR, ¹³C NMR and EIMS) data. ^dAs determined by HPLC, Daicel Chiralcel OD-H Column.

with 88-95% enantiomeric excess (ee). The diastereomeric ratios in the crude isolates were checked by ¹H NMR to note any inadvertent alteration of these ratios during subsequent purification. The crude isolates of **4** were found to be a diastereomeric mixture containing 92-97% of the *trans* isomer. The diastereoselectivity was determined by ¹H NMR spectroscopy and ee by chiral HPLC. In the *trans* isomers **4**, 6-H and 7-H are axial as indicated by their coupling constant ($J_{6,7} = 9.7$ Hz, J_{trans} ; the *cis* coupling constant $J_{6,7} = 4.3$ Hz). The absence of any measurable NOE between 6-H and 7-H also supports the *trans* stereochemistry of the compounds **4**.

The formation of **4** is rationalized by the Michael addition of rhodanines (**3**) to arylidene of oxathiolan-5-one (**6**), formed *in situ*, to furnish adducts **5** which undergo intramolecular nucleophilic attack of the oxygen atom (of the OH) at the carbonyl carbon (C-5) of the oxathiolan-5-one nucleus to yield **4** with the elimination of acetophenone (Scheme 2, Route A). This conclusion is based on the observation that the representative intermediate compounds **5a**, **5e** and **5h** could be isolated in 45-52% yield with 91-95% ee, these could be converted into the corresponding annulated products **4a**, **4e** and **5h** in quantitative yield, and that acetophenone was formed during the reaction (Scheme 2). The formation of adducts **5** and their annulation to **4** were highly diastereoselective in favour of *trans* isomers.

In a reaction mixture containing an equimolar **1**, **2** and **3**, more reactive **1** and **2** exclusively react to give arylidene **6** (Scheme 2, Route A), instead of the reaction of **2** and **3** to give **7** (Scheme 2, Route B) under the present reaction conditions. This is supported by the observation that the reaction of equimolar mixture of **1**, **2** and **3** in Pro₂SO₄ for 10-12 h afforded only **6** in 90-94% yields but not **7**. Thus, arylidene **6** is first formed only then relatively slower Michael addition of **3** to **6** takes place to afford **4** as the sole product through isolable intermediates **5** (Scheme 2, Route A). However, when a mixture of **2** and **3** in Pro₂SO₄ was stirred at r.t. for ~15 h, **7** is obtained in 80-85% yields which on treatment with **1** afforded **4** in 71-84% yields through **5** (Scheme 2, Route B).

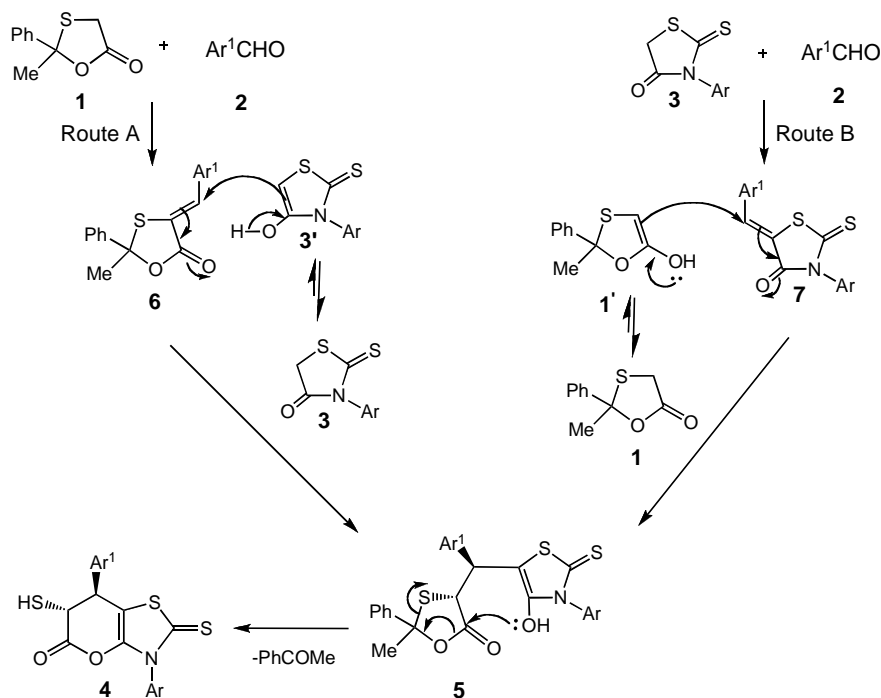
Thus, we have developed a general method for mild, rapid and efficient enantio- and diastereoselective route to potentially, pharmaceutically and agrochemically useful multifunctionalized pyranothiazoles using a chiral ionic liquid, L-prolinium sulfate (Pro₂SO₄), as the reaction medium and catalyst both.

EXPERIMENTAL

Melting points were determined by open glass capillary method and are uncorrected. IR spectra in KBr were recorded on a Perkin-Elmer 993 IR spectrophotometer. ¹H NMR spectra

Scheme 2

Postulated intermediates leading to products 4.



were recorded on a Bruker WM-40 C (400 MHz) FT spectrometer in DMSO- d_6 using TMS as internal reference. ^{13}C NMR spectra were recorded on the same instrument at 100 MHz using the same solvent and internal reference. Mass spectra were recorded on a JEOL D-300 mass spectrometer. Elemental analyses were carried out in a Coleman automatic carbon, hydrogen and nitrogen analyzer. Enantiomeric excess (ee) was determined by HPLC, using Daicel Chiralcel OD-H column. All chemicals used were reagent grade and were used as received without further purification. Silica gel-G was for TLC.

General procedure for the preparation of *trans*-3,7-diaryl-2,3,6,7-tetrahydro-6-mercapto-2-thioxopyrano[2,3-*d*]thiazol-5-one (4). Thoroughly mixed 2-methyl-2-phenyl-1,3-oxathiolan-5-one (**1**) (2.0 mmol), aromatic aldehyde **2** (2.0 mmol), 3-arylrhodanine **3** (2.0 mmol) and L-prolinium sulfate (0.2 mmol) in 10 mL THF was stirred at r.t. for 25-30 h. After completion of the reaction as indicated by TLC, 20 mL of water was added, and the product was extracted with EtOAc (3 \times 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated under vacuum to afford the crude product, which was purified by silica gel column chromatography (hexane-EtOAc, 3:1) to obtain an analytically pure sample of a single diastereomer in 76-90% yield with 88-95% ee (as determine by HPLC, Daicel Chiralcel OD-H, hexane/isopropanol 80:2, flow rate 0.8 mL/min). The crude product was found to be a diastereomeric mixture containing 92-97% of the *trans* isomer as determined by ^1H NMR spectroscopy. On the basis of comparison of *J* values with literature values [40-46], the *trans* stereochemistry was assigned to **4**, as the coupling constant ($J_{6,7} = 9.7$ Hz) of the major *trans* isomer was higher than that for the minor *cis* diastereomer ($J_{6,7} = 4.3$ Hz).

***trans*-2,3,6,7-Tetrahydro-6-mercapto-3,7-diphenyl-2-thioxopyrano[2,3-*d*]thiazol-5-one (4a).** Yellowish needles (ethanol), mp 129-130 $^\circ\text{C}$; ir: 3046, 2549, 1774, 1605, 1583, 1455 cm^{-1} ; ^1H NMR (DMSO- d_6 /TMS): δ 1.55 (d, $J = 8.2$ Hz, 1H, SH, exchangeable with D_2O), 6.57 (d, $J = 9.7$ Hz, 1H, 7-H), 6.65 (dd, $J = 9.7, 8.2$ Hz, 1H, 6-H), 7.12-8.85 (m, 10 H_{arom}); ^{13}C NMR (DMSO- d_6 /TMS): $\delta = 26.5$ (6-C), 43.8 (7-C), 127.2, 127.9, 128.6, 130.0, 130.8, 132.2, 133.0, 135.8 (2 \times Ph), 161.4 (C=C), 172.3 (C=O), 192.5 (C=S); ms: m/z 371 (M^+). *Anal.* Calcd. For $\text{C}_{18}\text{H}_{13}\text{NO}_2\text{S}_3$: C, 58.20; H, 3.53; N, 3.77. Found: C, 58.51; H, 3.35; N, 3.61.

***trans*-7-(4-Chlorophenyl)-2,3,6,7-tetrahydro-6-mercapto-3-phenyl-2-thioxopyrano[2,3-*d*]thiazol-5-one (4b).** Yellowish needles (ethanol), mp 199-201 $^\circ\text{C}$; ir: 3047, 2555, 1773, 1601, 1588, 1456 cm^{-1} ; ^1H NMR (DMSO- d_6 /TMS): δ 1.59 (d, $J = 8.2$ Hz, 1H, SH, exchangeable with D_2O), 6.58 (d, $J = 9.7$ Hz, 1H, 7-H), 6.67 (dd, $J = 9.7, 8.2$ Hz, 1H, 6-H), 7.10-8.75 (m, 9 H_{arom}); ^{13}C NMR (DMSO- d_6 /TMS): $\delta = 25.9$ (6-C), 44.0 (7-C), 127.3, 128.0, 128.6, 129.7, 130.6, 131.8, 132.9, 133.6 (Ph, 4-ClC $_6$ H $_4$), 161.8 (C=C), 172.6 (C=O), 192.7 (C=S); ms: m/z 405, 407 (M^+ , $\text{M}^+ + 2$). *Anal.* Calcd. For $\text{C}_{18}\text{H}_{12}\text{ClNO}_2\text{S}_3$: C, 53.26; H, 2.98; N, 3.45. Found: C, 53.55; H, 3.23; N, 3.30.

***trans*-2,3,6,7-Tetrahydro-6-mercapto-7-(4-methoxyphenyl)-3-phenyl-2-thioxopyrano[2,3-*d*]thiazol-5-one (4c).** Yellowish needles (ethanol), mp 131-132 $^\circ\text{C}$; ir: 3042, 2543, 1771, 1598, 1579, 1451 cm^{-1} ; ^1H NMR (DMSO- d_6 /TMS): δ 1.54 (d, $J = 8.2$ Hz, 1H, SH, exchangeable with D_2O), 3.75 (s, 3H, OMe), 6.55 (d, $J = 9.7$ Hz, 1H, 7-H), 6.64 (dd, $J = 9.7, 8.2$ Hz, 1H, 6-H), 7.11-8.81 (m, 9 H_{arom}); ^{13}C NMR (DMSO- d_6 /TMS): $\delta = 26.4$ (6-C), 43.6 (7-C), 54.3 (OMe), 127.0, 128.1, 128.8, 129.9, 130.8, 131.6, 132.8, 133.5 (Ph, 4-MeOC $_6$ H $_4$), 161.3 (C=C), 172.1 (C=O), 192.3 (C=S); ms: m/z 401 (M^+). *Anal.*

Calcd. For $C_{19}H_{15}NO_3S_3$: C, 56.83; H, 3.77; N, 3.49. Found: C, 56.53; H, 3.57; N, 3.62.

trans-2,3,6,7-Tetrahydro-6-mercapto-3-(2-methoxyphenyl)-7-phenyl-2-thioxopyrano[2,3-d]thiazol-5-one (4d). Yellowish needles (ethanol), mp 109-111 °C; ir: 3043, 2548, 1774, 1602, 1577, 1454 cm^{-1} ; 1H NMR (DMSO- d_6 /TMS): δ 1.55 (d, J = 8.2 Hz, 1H, SH, exchangeable with D_2O), 3.74 (s, 3H, OMe), 6.57 (d, J = 9.7 Hz, 1H, 7-H), 6.63 (dd, J = 9.7, 8.2 Hz, 1H, 6-H), 7.21-8.86 (m, 9H_{arom}); ^{13}C NMR (DMSO- d_6 /TMS): δ = 26.3 (6-C), 43.7 (7-C), 54.2 (OMe), 126.7, 127.5, 128.6, 129.3, 130.6, 131.2, 132.2, 132.9, 133.5, 134.3 (Ph, 2-MeOC₆H₄), 161.2 (C=C), 172.4 (C=O), 192.2 (C=S); ms: m/z 401 (M⁺). *Anal.* Calcd. For $C_{19}H_{15}NO_3S_3$: C, 56.83; H, 3.77; N, 3.49. Found: C, 57.03; H, 3.92; N, 3.34.

trans-7-(4-Chlorophenyl)-2,3,6,7-tetrahydro-6-mercapto-3-(2-methoxyphenyl)-2-thioxopyrano[2,3-d]thiazol-5-one (4e). Yellowish needles (ethanol), mp 91-92 °C; ir: 3046, 2552, 1775, 1606, 1581, 1455 cm^{-1} ; 1H NMR (DMSO- d_6 /TMS): δ 1.58 (d, J = 8.2 Hz, 1H, SH, exchangeable with D_2O), 3.77 (s, 3H, OMe), 6.61 (d, J = 9.7 Hz, 1H, 7-H), 6.69 (dd, J = 9.7, 8.2 Hz, 1H, 6-H), 7.18-8.80 (m, 8H_{arom}); ^{13}C NMR (DMSO- d_6 /TMS): δ = 26.8 (6-C), 43.9 (7-C), 54.5 (OMe), 126.8, 127.7, 128.5, 129.3, 130.6, 131.4, 132.0, 132.7, 133.5, 135.3 (2-MeOC₆H₄, 4-ClC₆H₄), 161.5 (C=C), 172.5 (C=O), 192.2 (C=S); ms: m/z 435, 437 (M⁺, M⁺ + 2). *Anal.* Calcd. For $C_{19}H_{14}ClNO_3S_3$: C, 52.34; H, 3.24; N, 3.21. Found: C, 52.60; H, 3.45; N, 3.11.

trans-2,3,6,7-Tetrahydro-6-mercapto-3-(2-methoxyphenyl)-7-(4-methoxyphenyl)-2-thioxopyrano[2,3-d]thiazol-5-one (4f). Yellowish needles (ethanol), mp 114-115 °C; ir: 3043, 2548, 1772, 1599, 1578, 1449 cm^{-1} ; 1H NMR (DMSO- d_6 /TMS): δ 1.52 (d, J = 8.2 Hz, 1H, SH, exchangeable with D_2O), 3.72 (s, 3H, OMe), 3.79 (s, 3H, OMe), 6.52 (d, J = 9.7 Hz, 1H, 7-H), 6.65 (dd, J = 9.7, 8.2 Hz, 1H, 6-H), 7.15-8.79 (m, 8H_{arom}); ^{13}C NMR (DMSO- d_6 /TMS): δ = 26.5 (6-C), 43.5 (7-C), 54.2, 54.9 (2 x OMe), 126.8, 127.6, 128.5, 129.2, 130.5, 131.3, 132.1, 132.8, 133.6, 134.3, (2-MeOC₆H₄, 4-MeOC₆H₄), 161.3 (C=C), 172.1 (C=O), 192.3 (C=S); ms: m/z 431 (M⁺). *Anal.* Calcd. For $C_{20}H_{17}NO_4S_3$: C, 55.66; H, 3.97; N, 3.25. Found: C, 55.93; H, 3.72; N, 3.36.

trans-2,3,6,7-Tetrahydro-6-mercapto-3-(4-methoxyphenyl)-7-phenyl-2-thioxopyrano[2,3-d]thiazol-5-one (4g). Yellowish needles (ethanol), mp 119-121 °C; ir: 3042, 2550, 1775, 1597, 1580, 1447 cm^{-1} ; 1H NMR (DMSO- d_6 /TMS): δ 1.53 (d, J = 8.2 Hz, 1H, SH, exchangeable with D_2O), 3.69 (s, 3H, OMe), 6.53 (d, J = 9.7 Hz, 1H, 7-H), 6.67 (dd, J = 9.7, 8.2 Hz, 1H, 6-H), 7.18-8.78 (m, 9H_{arom}); ^{13}C NMR (DMSO- d_6 /TMS): δ = 26.3 (6-C), 43.6 (7-C), 54.3 (OMe), 126.2, 128.0, 129.3, 130.6, 131.3, 132.2, 133.7, 134.5 (Ph, 4-MeOC₆H₄), 161.5 (C=C), 172.2 (C=O), 192.6 (C=S); ms: m/z 401 (M⁺). *Anal.* Calcd. For $C_{19}H_{15}NO_3S_3$: C, 56.83; H, 3.77; N, 3.49. Found: C, 57.12; H, 3.63; N, 3.59.

trans-7-(4-Chlorophenyl)-2,3,6,7-tetrahydro-6-mercapto-3-(4-methoxyphenyl)-2-thioxopyrano[2,3-d]thiazol-5-one (4h). Yellowish needles (ethanol), mp 103-105 °C; ir: 3045, 2553, 1777, 1603, 1585, 1450 cm^{-1} ; 1H NMR (DMSO- d_6 /TMS): δ 1.56 (d, J = 8.2 Hz, 1H, SH, exchangeable with D_2O), 3.75 (s, 3H, OMe), 6.57 (d, J = 9.7 Hz, 1H, 7-H), 6.68 (dd, J = 9.7, 8.2 Hz, 1H, 6-H), 7.50-8.75 (m, 8H_{arom}); ^{13}C NMR (DMSO- d_6 /TMS): δ = 27.0 (6-C), 44.2 (7-C), 54.8 (OMe), 126.9, 128.4, 129.0, 130.1, 132.0, 132.7, 133.3, 134.2 (4-MeOC₆H₄, 4-ClC₆H₄), 161.8 (C=C), 172.7 (C=O), 192.8 (C=S); ms: m/z 435, 437 (M⁺, M⁺ + 2). *Anal.* Calcd. For $C_{19}H_{14}ClNO_3S_3$: C, 52.34; H, 3.24; N, 3.21. Found: C, 52.69; H, 3.09; N, 3.32.

trans-2,3,6,7-Tetrahydro-6-mercapto-3,7-bis(4-methoxyphenyl)-2-thioxopyrano[2,3-d]thiazol-5-one (4i). Yellowish needles (ethanol), mp 143-145 °C; ir: 3044, 2550, 1773, 1598, 1581, 1452 cm^{-1} ; 1H NMR (DMSO- d_6 /TMS): δ 1.51 (d, J = 8.2 Hz, 1H, SH, exchangeable with D_2O), 3.71 (s, 3H, OMe), 3.77 (s, 3H, OMe), 6.50 (d, J = 9.7 Hz, 1H, 7-H), 6.63 (dd, J = 9.7, 8.2 Hz, 1H, 6-H), 7.09-7.98 (m, 8H_{arom}); ^{13}C NMR (DMSO- d_6 /TMS): δ = 26.1 (6-C), 43.3 (7-C), 54.0, 54.7 (2 x OMe), 127.8, 129.0, 131.2, 132.1, 132.9, 133.5, 134.3, 135.5 (2 x 4-MeOC₆H₄), 161.2 (C=C), 172.4 (C=O), 192.3 (C=S); ms: m/z 431 (M⁺). *Anal.* Calcd. For $C_{20}H_{17}NO_4S_3$: C, 55.66; H, 3.97; N, 3.25. Found: C, 55.38; H, 3.78; N, 3.48.

trans-2,3,6,7-Tetrahydro-6-mercapto-7-phenyl-2-thioxo-3-o-tolylpyrano[2,3-d]thiazol-5-one (4j). Yellowish needles (ethanol), mp 130-132 °C; ir: 3045, 2549, 1774, 1604, 1583, 1451 cm^{-1} ; 1H NMR (DMSO- d_6 /TMS): δ 1.53 (d, J = 8.2 Hz, 1H, SH, exchangeable with D_2O), 2.30 (s, 3H, Me), 6.57 (d, J = 9.7 Hz, 1H, 7-H), 6.67 (dd, J = 9.7, 8.2 Hz, 1H, 6-H), 7.08-8.75 (m, 9H_{arom}); ^{13}C NMR (DMSO- d_6 /TMS): δ = 21.6 (Me), 26.6 (6-C), 43.9 (7-C), 126.8, 127.6, 128.5, 129.2, 130.5, 131.3, 132.1, 132.8, 133.6, 134.3 (Ph, 2-MeC₆H₄), 161.4 (C=C), 172.3 (C=O), 192.5 (C=S); ms: m/z 385 (M⁺). *Anal.* Calcd. For $C_{19}H_{15}NO_2S_3$: C, 59.19; H, 3.92; N, 3.63. Found: C, 59.49; H, 3.79; N, 3.73.

trans-7-(4-Chlorophenyl)-2,3,6,7-tetrahydro-6-mercapto-2-thioxo-3-o-tolylpyrano[2,3-d]thiazol-5-one (4k). Yellowish needles (ethanol), mp 126-127 °C; ir: 3044, 2552, 1771, 1601, 1578, 1446 cm^{-1} ; 1H NMR (DMSO- d_6 /TMS): δ 1.56 (d, J = 8.2 Hz, 1H, SH, exchangeable with D_2O), 2.35 (s, 3H, Me), 6.60 (d, J = 9.7 Hz, 1H, 7-H), 6.71 (dd, J = 9.7, 8.2 Hz, 1H, 6-H), 7.12-8.82 (m, 8H_{arom}); ^{13}C NMR (DMSO- d_6 /TMS): δ = 21.7 (Me), 26.8 (6-C), 44.0 (7-C), 126.7, 127.4, 128.3, 129.1, 130.1, 131.2, 132.3, 132.9, 133.7, 135.7 (2-MeC₆H₄, 4-ClC₆H₄), 161.5 (C=C), 172.5 (C=O), 192.6 (C=S); 419, 421 (M⁺, M⁺ + 2). *Anal.* Calcd. For $C_{19}H_{14}ClNO_2S_3$: C, 54.34; H, 3.36; N, 3.34. Found: C, 54.54; H, 3.56; N, 3.25.

trans-2,3,6,7-Tetrahydro-6-mercapto-7-(4-methoxyphenyl)-2-thioxo-3-o-tolylpyrano[2,3-d]thiazol-5-one (4l). Yellowish needles (ethanol), mp 121-123 °C; ir: 3042, 2548, 1775, 1599, 1581, 1454 cm^{-1} ; 1H NMR (DMSO- d_6 /TMS): δ 1.54 (d, J = 8.2 Hz, 1H, SH, exchangeable with D_2O), 2.33 (s, 3H, Me), 3.75 (s, 3H, OMe), 6.59 (d, J = 9.7 Hz, 1H, 7-H), 6.68 (dd, J = 9.7, 8.2 Hz, 1H, 6-H), 7.10-8.78 (m, 8H_{arom}); ^{13}C NMR (DMSO- d_6 /TMS): δ = 21.4 (Me), 26.3 (6-C), 43.6 (7-C), 54.8 (OMe), 126.6, 127.5, 128.3, 128.9, 129.9, 131.1, 131.8, 132.6, 133.4, 134.2 (2-MeC₆H₄, 4-MeOC₆H₄), 161.5 (C=C), 172.6 (C=O), 192.7 (C=S); ms: m/z 415 (M⁺). *Anal.* Calcd. For $C_{20}H_{17}NO_3S_3$: C, 57.81; H, 4.12; N, 3.37. Found: C, 58.10; H, 4.32; N, 3.25.

General procedure for isolation of Michael adducts 5a, 5e and 5h and their conversion into the corresponding annulated products 4a, 4e and 4h. The procedure followed was the same as described above for the synthesis of **4** except that the time of stirring in this case was 10-16 h instead of 25-30 h for **4**. The adducts **5** were purified by silica gel column chromatography (hexane-EtOAc, 3:1) to obtain an analytically pure sample of **5** in 43-55% yield with 85-93% ee. The crude product was found to be a diastereomeric mixture containing 91-96% of the *trans* isomer as determined by 1H NMR spectroscopy. The adducts **5** were assigned the *trans* stereochemistry as their 1H NMR spectra exhibited higher values of coupling constant, $J_{SCH,acyclicCH} = 9.5$ Hz, than that of *cis* diastereomer, $J_{SCH,acyclicCH} = 4.6$ Hz [40-46]. The intermediate compound **5a**, **5e** or **5h** (2.0 mmol) and L-prolinium sulfate (0.2

mmol) in 7 mL of THF was stirred at r.t. for 9-13 h to give the corresponding products **4a**, **4e** or **4h** quantitatively. These were isolated and purified in the same way as described above for compounds **4**.

trans-(2,3-Dihydro-4-hydroxy-3-phenyl-2-thioxothiazol-5-yl)(phenyl)methyl-2-methyl-2-phenyl-1,3-oxathiolan-5-one (5a). Pale yellow solid (ethanol), mp 151-154 °C; ir: 3388, 3043, 1771, 1602, 1581, 1449 cm⁻¹; ¹H NMR (DMSO-*d*₆/TMS): δ 2.31 (s, 3H, Me), 6.35 (br s, 1H, OH, exchangeable with D₂O), 6.61 (d, J = 9.5 Hz, 1H, 7-H), 6.72 (d, J = 9.5 Hz, 1H, 6-H), 7.16-8.23 (m, 15H_{arom}); ¹³C NMR (DMSO-*d*₆/TMS): δ = 20.5 (Me), 35.6 (Ar¹-C), 51.9 (SCH), 75.4 (S=CS-C), 112.2 (O=CO-C), 126.5, 127.3, 128.5, 130.0, 131.8, 132.5, 133.2, 134.7 (2 × Ph), 172.2 (C=O), 185.5 (OH-C), 192.1 (C=S); ms: m/z 491 (M⁺). *Anal.* Calcd. For C₂₆H₂₁NO₃S₃: C, 63.52; H, 4.31; N, 2.85. Found: C, 63.29; H, 4.47; N, 2.71.

trans-(3-(4-Chlorophenyl)-2,3-dihydro-4-hydroxy-2-thioxothiazol-5-yl)(2-methoxyphenyl)methyl-2-methyl-2-phenyl-1,3-oxathiolan-5-one (5e). Pale yellow solid (ethanol), mp 117-119 °C; ir: 3389, 3045, 1770, 1605, 1585, 1446 cm⁻¹; ¹H NMR (DMSO-*d*₆/TMS): δ 2.31 (s, 3H, Me), 3.72 (s, 3H, OMe), 6.38 (br s, 1H, OH, exchangeable with D₂O), 6.60 (d, J = 9.5 Hz, 1H, 7-H), 6.76 (d, J = 9.5 Hz, 1H, 6-H), 7.19-8.19 (m, 13H_{arom}); ¹³C NMR (DMSO-*d*₆/TMS): δ = 20.7 (Me), 35.9 (Ar¹-C), 52.3 (SCH), 54.3 (OMe), 75.5 (S=CS-C), 112.7 (O=CO-C), 126.3, 127.1, 127.9, 128.7, 130.0, 130.7, 131.5, 132.1, 133.0, 133.7 (2-MeOC₆H₄, 4-ClC₆H₄), 172.8 (C=O), 185.3 (OH-C), 192.4 (C=S); ms: m/z 555, 557 (M⁺, M⁺ + 2). *Anal.* Calcd. For C₂₇H₂₂ClNO₄S₃: C, 58.31; H, 3.99; N, 2.52. Found: C, 58.67; H, 3.78; N, 2.43.

trans-(3-(4-Chlorophenyl)-2,3-dihydro-4-hydroxy-2-thioxothiazol-5-yl)(4-methoxyphenyl)methyl-2-methyl-2-phenyl-1,3-oxathiolan-5-one (5h). Pale yellow solid (ethanol), mp 129-131 °C; ir: 3386, 3042, 1772, 1601, 1588, 1448 cm⁻¹; ¹H NMR (DMSO-*d*₆/TMS): δ 2.33 (s, 3H, Me), 3.73 (s, 3H, OMe), 6.37 (br s, 1H, OH, exchangeable with D₂O), 6.63 (d, J = 9.5 Hz, 1H, 7-H), 6.78 (d, J = 9.5 Hz, 1H, 6-H), 7.21-8.27 (m, 13H_{arom}); ¹³C NMR (DMSO-*d*₆/TMS): δ = 21.2 (Me), 35.8 (Ar¹-C), 52.7 (SCH), 54.7 (OMe), 75.4 (S=CS-C), 112.8 (O=CO-C), 126.8, 127.7, 128.7, 130.5, 131.8, 132.4, 133.2, 134.1 (4-MeOC₆H₄, 4-ClC₆H₄), 172.6 (C=O), 185.6 (OH-C), 192.5 (C=S); ms: m/z 555, 557 (M⁺, M⁺ + 2). *Anal.* Calcd. For C₂₇H₂₂ClNO₄S₃: C, 58.31; H, 3.99; N, 2.52. Found: C, 58.23; H, 3.81; N, 2.83.

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