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# Chiral ionic liquid-catalyzed Biginelli reaction: stereoselective synthesis of polyfunctionalized perhydropyrimidines

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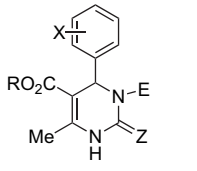
**Abstract**

A chiral ionic liquid-catalyzed, efficient and unprecedented version of the Biginelli reaction using new variants of its active methylene component, viz. 2-phenyl-1,3-oxazol-5-one/2-methyl-2-phenyl-1,3-oxathiolan-5-one, with aromatic aldehydes and urea/thiourea enantio- and diastereoselectively, yields 5-amino-/mercaptoperhydropyrimidines. This three-component domino cyclocondensation reaction is effected via ring transformation of an isolable intermediate in a one-pot procedure.


*Keywords:* Ionic liquids; Perhydropyrimidines; Stereoselective synthesis; Biginelli reaction; Oxazolone; Oxathiolanone

## 1. Introduction

FDA approved dihydropyridine (DHP) derivatives Nifedipine, Nicardipine and Amlodipine have become almost indispensable for the treatment of cardiovascular diseases such as hypertension, cardiac arrhythmias, or angina.[1] Consequently, interest has also been focused on their aza-analogues such as dihydropyrimidine (DHPM) derivatives (Fig. 1), which are superior in potency and duration of antihypertensive activity to classical calcium channel modulator DHP drugs and compare favourably with second-generation drugs Nicardipine and Amlodipine.[2,3] Furthermore, monastrol and various marine natural products incorporating DHPM scaffolds are valuable new leads for the development of anticancer and AIDS therapy.[4,5]




R = alkyl, Z = O, S
X = 2-/3-$NO_2$, 2-$CF_3$
E = ester, acyl, amide

Figure 1.

The amino and mercapto functions are synthetically and pharmacologically readily manipulable. Perhydropyrimidine scaffolds incorporating the $-NH_2$ and $-SH$ functions are hitherto unreported and are not accessible through any one of the known synthetic routes although they appear as attractive scaffolds to be utilized for exploiting chemical diversity and generating a drug-like library to screen for lead candidates.

The Biginelli reaction[6] is one of the fundamental one-pot three-component cyclocondensation strategies for the synthesis of DHPM scaffolds. In the last two decades, more efficient conditions have been found for the Biginelli reaction using soft Lewis acids as catalyst.[7] Microwave irradiation[8] as well as solid-phase and fluoro-phase techniques[9] facilitating this synthesis have also become increasingly widespread. In over 110 years of study of the Biginelli reaction, only minor structural variations in all the three building blocks have been reported[10,11] apart from a very recently reported major structural variation where the urea component was replaced by a guanidine system.[12] However, to the best of our knowledge,

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there has been no such major variation in the active methylene building block, this could be a significant and useful extension of the Biginelli reaction for the synthesis of polyfunctionalized perhydropyrimidines.

Ionic liquids (ILs) have attracted increasing interest in the context of green chemistry owing to their great potential as environmentally benign reaction media.[13–16] Now ILs have marched far beyond the border of solvent showing their significant roles in controlling the reaction as new catalysts[16–18] and reagents.[19,20] A recent review[21] presents studies on the application of chiral ionic liquids (CILs) not only as an opportunity but also as a challenge for researchers. Although a few examples of the application of achiral ILs in the Biginelli reaction are available in the literature,[22,23] we are unaware of the use of a chiral IL in this reaction. The chiral ionic liquids L-prolinium sulfate ($Pro_2SO_4$), L-alaninium hexafluorophosphate ($AlaPF_6$) and L-threoninium nitrate ($ThrNO_3$), which we have used in the present study, are directly obtainable from a natural α-amino acid.[24] The present work is of particular importance in the context of green chemistry whose principles include the utilization of biorenewable resources. The reason for which we have been spurred to use chiral ionic liquids in the Biginelli reaction stems from the desire to achieve a degree of asymmetric induction and thus obtain enantio- and diastereomerically pure perhydropyrimidines as the biological activity of DHPMs is strictly dependent on the absolute configuration at the C-4 stereocentre.[10,25]

Prompted by the above valid points and as part of our continuous drive to devise new stereoselective cyclization processes,[26–30] we decided to investigate the potential of chiral ionic liquids to accelerate the Biginelli reaction for the enantio- and diastereoselective synthesis of polyfunctionalized perhydropyrimidines employing 2-phenyl-1,3-oxazol-5-one and a recently reported[29] mercaptoacetyl transfer agent, 2-methyl-2-phenyl-1,3-oxathiolan-5-one (Fig. 2), as new variants of the active methylene building block in this venerable reaction (Schemes 1 and 2).

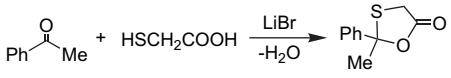
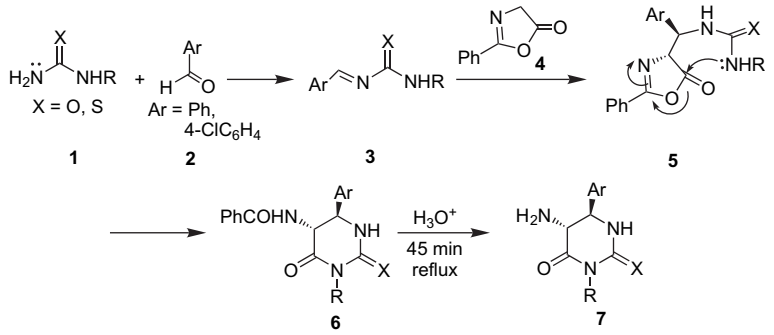



Figure 2. Preparation of mercaptoacetyl transfer agent 2-methyl-2-phenyl-1,3-oxathiolan-5-one.

Interestingly, the unprecedented variants of the Biginelli reaction reported herein yielding polyfunctionalized perhydropyrimidines with high enantio- and diastereoselectivity represent the first example of this venerable reaction catalyzed by a chiral ionic liquid.

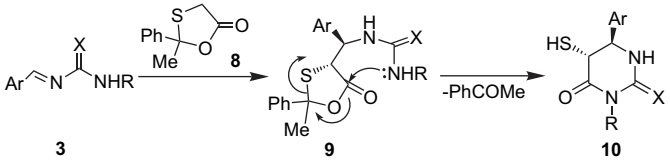
## 2. Results and discussion

The envisaged strategy for the major variation in the active methylene building block of the Biginelli reaction was successful by stirring a mixture of either 2-phenyl-1,3-oxazol-5-one **4** (Scheme 1) or 2-methyl-2-phenyl-1,3-oxathiolan-5-one **8** (Scheme 2) with urea/thiourea **1**, an aromatic aldehyde **2** and $Pro_2SO_4$ in THF at room temperature for 21–30 h. Isolation and purification by column chromatography afforded perhydropyrimidines as a single diastereomer **6** in 80–92% yields with 81–94% enantiomeric excess (ee), and **10** in 82–93% yields with 78–95% ee. Under conventional reaction conditions[31] and using other CILs ($AlaPF_6$ and $ThrNO_3$) these new reagents **4** and **8** afforded the same perhydropyrimidines in relatively lower yields (41–53%), with significantly lower stereoselectivity (ee 48–57%) and slightly lower trans diastereoselectivity (89–93%). The diastereomeric ratios in the crude isolates were checked by $^1$H NMR spectroscopy to note any inadvertent alteration of these ratios during subsequent purification. The crude isolates of **6** and **10** were found to be a diastereomeric mixture containing 91–95% and 92–97% of the trans isomer, respectively. The diastereoselectivity was determined by $^1$H NMR spectroscopy and ee by chiral HPLC. In the trans isomers **6** and **10**, 5-H and 6-H are axial as indicated by their coupling constant ($J_{5,6}$=9.2 Hz, $J_{trans}$; the cis coupling constant $J_{5,6}$=3.9 Hz). The absence of any measurable NOE between 5-H and 6-H also supports the trans stereochemistry of the compounds **6** and **10**.




| 3,5-7 | R | Ar | X | 3,5-7 | R | Ar | X |
|---|---|---|---|---|---|---|---|
| **a** | H | Ph | O | **e** | 2-MeC$_6$H$_4$ | Ph | O |
| **b** | H | Ph | S | **f** | Et | Ph | O |
| **c** | Ph | Ph | O | **g** | H | 4-ClC$_6$H$_4$ | O |
| **d** | Ph | Ph | S | **h** | H | 4-ClC$_6$H$_4$ | S |

Scheme 1. Tentative mechanism for the formation of 5-aminoperhydropyridines **7**.

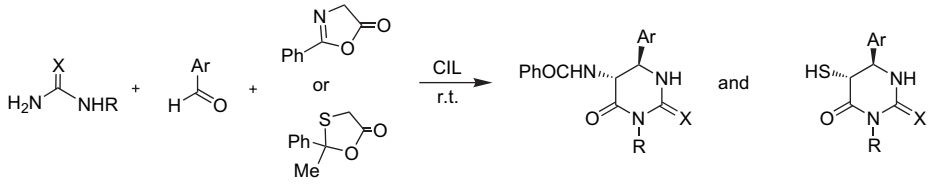



| 3,9,10 | R | Ar | X | 3,9,10 | R | Ar | X |
|---|---|---|---|---|---|---|---|
| **a** | H | Ph | O | **e** | 2-MeC$_6$H$_4$ | Ph | O |
| **b** | H | Ph | S | **f** | Et | Ph | O |
| **c** | Ph | Ph | O | **g** | H | 4-ClC$_6$H$_4$ | O |
| **d** | Ph | Ph | S | **h** | H | 4-ClC$_6$H$_4$ | S |

Scheme 2. Tentative mechanism for the formation of 5-mercaptoperhydropyridines **10**.

The formation of **6** and **10** may tentatively be rationalized by a mechanism in agreement with that of the Biginelli reaction[32] where the adducts **5** and **9** undergo intramolecular nucleophilic attack of the nitrogen atom of the urea/thiourea moiety at the carbonyl carbon (C-5) of the oxathiolan-5-one and oxazol-5-one nuclei to yield **6** and **10**, respectively (Schemes 1 and 2). It was noticed that acetophenone, which was used to activate mercaptoacetic acid to act as a novel and efficient active methylene building block **8**, is automatically removed during the reactions yielding compounds **10** (Scheme 2). These conclusions are based on the observation that the representative intermediate compounds **5a**, **5c**, **5e**,

Table 1
Chiral ionic liquid ($Pro_2SO_4$)-catalyzed synthesis of **5**, **6**, **9** and **10** at room temperature



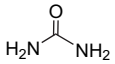
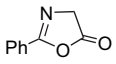
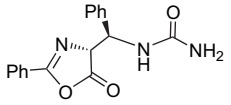
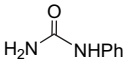
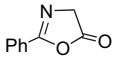
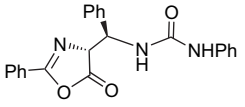
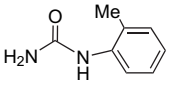
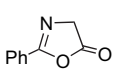
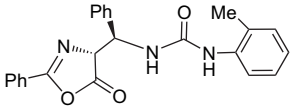
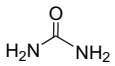
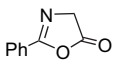
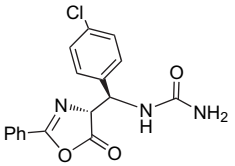
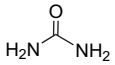
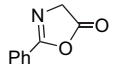
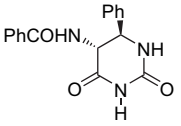
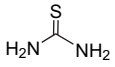
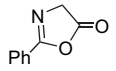
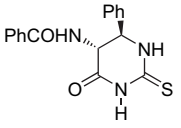
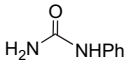
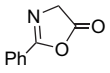
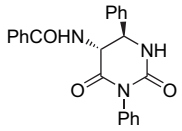
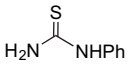
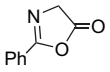
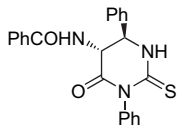
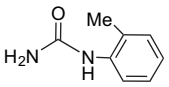
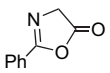
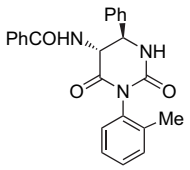
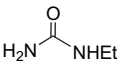
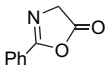
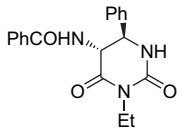
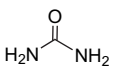
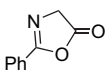
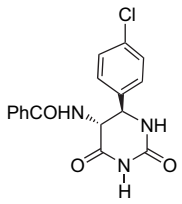
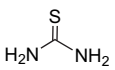
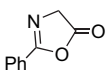
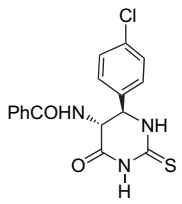
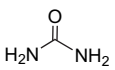
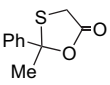
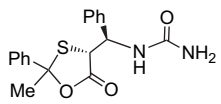
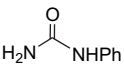
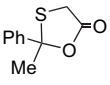
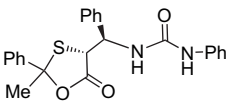
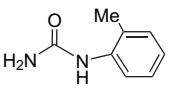
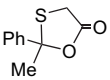
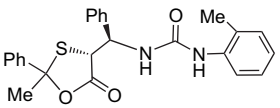
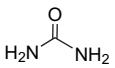
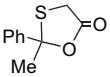
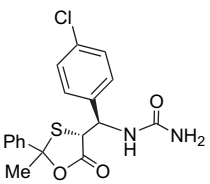
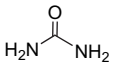
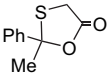
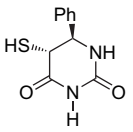
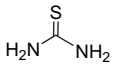
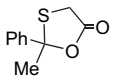
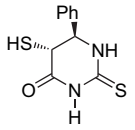
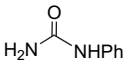
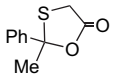
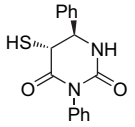
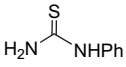
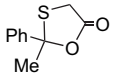
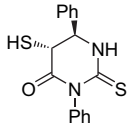
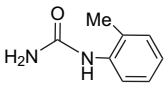
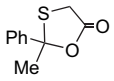
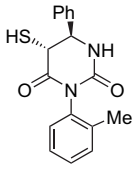
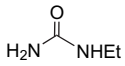
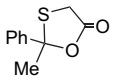
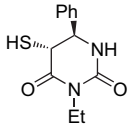
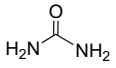
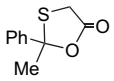
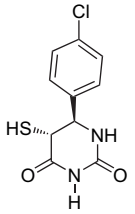
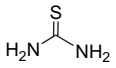
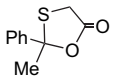
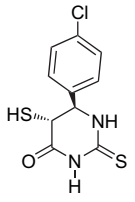

| Compound | Urea/thiourea | Active methylene component | Product | Time[a] (h) | Yield[b,c] (%) | ee[d] |
|---|---|---|---|---|---|---|
| **5a** |  |  |  | 12 | 51 | 91 |
| **5c** |  |  |  | 10 | 45 | 95 |
| **5e** |  |  |  | 15 | 42 | 82 |
| **5g** |  |  |  | 12 | 48 | 89 |
| **6a** |  |  |  | 27 | 84 | 94 |
| **6b** |  |  |  | 23 | 91 | 91 |

Table 1 (*continued*)

| Compound | Urea/thiourea | Active methylene component | Product | Time[a] (h) | Yield[b,c] (%) | ee[d] |
|---|---|---|---|---|---|---|
| **6c** |  |  |  | 30 | 88 | 83 |
| **6d** |  |  |  | 22 | 80 | 90 |
| **6e** |  |  |  | 29 | 92 | 81 |
| **6f** |  |  |  | 21 | 84 | 87 |
| **6g** |  |  |  | 25 | 90 | 90 |
| **6h** |  |  |  | 28 | 87 | 94 |
| **9a** |  |  |  | 13 | 49 | 87 |
| **9c** |  |  |  | 15 | 52 | 94 |
| **9e** |  |  |  | 10 | 44 | 83 |
| **9g** |  |  |  | 12 | 51 | 91 |
| **10a** |  |  |  | 23 | 87 | 95 |

(*continued on next page*)

Table 1 (*continued*)

| Compound | Urea/thiourea | Active methylene component | Product | Time[a] (h) | Yield[b,c] (%) | ee[d] |
|---|---|---|---|---|---|---|
| **10b** |  |  |  | 29 | 90 | 79 |
| **10c** |  |  |  | 30 | 82 | 83 |
| **10d** |  |  |  | 24 | 85 | 87 |
| **10e** |  |  |  | 27 | 93 | 78 |
| **10f** |  |  |  | 21 | 83 | 91 |
| **10g** |  |  |  | 27 | 88 | 93 |
| **10h** |  |  |  | 24 | 91 | 82 |

[a] Stirring time at room temperature.
[b] Yield of isolated and purified products.
[c] All compounds gave C, H and N analyses within ±0.36% and satisfactory spectral (IR, $^1$H NMR, $^{13}$C NMR and EI-MS) data.
[d] As determined by HPLC, Daicel Chiralcel OD-H column.

**5g** and **9a**, **9c**, **9e**, **9g** could be isolated in 42–51% and 44–52% yields, respectively, and that these could be converted into the corresponding annulated products **6a**, **6c**, **6e**, **6g** and **10a**, **10c**, **10e**, **10g** in quantitative yield (Table 1).

## 3. Conclusion

In summary, we have developed a chiral ionic liquid-catalyzed unprecedented version of the Biginelli reaction using new variants of its active methylene component for an efficient enantio- and diastereoselective synthesis of polyfunctionalized perhydropyrimidine scaffolds of pharmacological potential in a one-pot procedure.

## 4. Experimental

### *4.1. General*

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 and $^1$H NMR spectra were recorded on a Bruker WM-40 C (400 MHz) FT

spectrometer in DMSO-$d_6$+$D_2O$ using TMS as internal reference. $^{13}C$ NMR spectra were recorded on the same instrument at 100 MHz in DMSO-$d_6$ and TMS was used as internal reference. Mass (EI) 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 a Daicel Chiralcel OD-H column. Retention time ($t_R$) is given in minutes. All chemicals used were of reagent grade and were used as received without further purification. Silica gel G was used for TLC.

### 4.2. 5-Benzamido-6-phenylperhydropyrimidines **6**: general procedure

A mixture of urea/thiourea **1** (2.0 mmol), an aromatic aldehyde **2** (2.0 mmol), 2-phenyl-1,3-oxazol-5-one **4** (2.0 mmol) and L-prolinium sulfate (0.2 mmol) in 8 mL of THF was stirred at room temperature for 21–30 h. After completion of the reaction as indicated by TLC, 20 mL of water was added and the product was extracted with EtOAc (3×20 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 **6** in 80–92% yield with 81–94% ee (as determined by HPLC, Daicel Chiralcel OD-H, hexane/isopropanol 80:20, flow rate 0.8 mL/min). The crude product was found to be a diastereomeric mixture containing 91–95% of the trans isomer as determined by $^1H$ NMR spectroscopy.

On the basis of comparison of $J$ values with literature values,[33–39] the trans stereochemistry was assigned to **6**, as the coupling constant ($J_{5,6}$=9.2 Hz) of the major trans isomer was higher than that for the minor cis diastereomer ($J_{5,6}$=3.9 Hz).

#### 4.2.1. Compound ***6a***

Yellowish needles (0.52 g, 84%), mp 126–128 °C. $[\alpha]_D^{20}$ −55.7 (*c* 0.5, MeOH), $t_R$=9.17 min. IR (KBr) $\nu_{max}$ 3345, 3310, 3048, 1735, 1705, 1680, 1605, 1585, 1455 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$+$D_2O$/TMS) $\delta$: 4.95 (d, 1H, $J$=9.2 Hz, H-6), 5.72 (d, 1H, $J$=9.2 Hz, H-5), 7.56–7.88 (m, $10H_{arom}$). $^{13}C$ NMR (DMSO-$d_6$/TMS) $\delta$: 61.2 (5-C), 62.8 (6-C), 126.7, 127.4, 128.2, 129.0, 129.7, 130.6, 131.2, 132.5 (2×Ph), 172.5, 173.3, 174.6 (3×C=O). Mass (*m/z*): 309 ($M^+$). Anal. Calcd for $C_{17}H_{15}N_3O_3$: C, 66.01; H, 4.89; N, 13.58%. Found: C, 65.79; H, 4.65; N, 13.83%.

#### 4.2.2. Compound ***6b***

Yellowish needles (0.59 g, 91%), mp 150–151 °C. $[\alpha]_D^{20}$ −62.2 (*c* 0.5, MeOH), $t_R$=8.65 min. IR (KBr) $\nu_{max}$ 3341, 3312, 3045, 1710, 1682, 1601, 1581, 1450, 1055 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$+$D_2O$/TMS) $\delta$: 4.98 (d, 1H, $J$=9.2 Hz, H-6), 5.70 (d, 1H, $J$=9.2 Hz, H-5), 7.31–7.78 (m, $10H_{arom}$). $^{13}C$ NMR (DMSO-$d_6$/TMS) $\delta$: 61.5 (5-C), 63.0 (6-C), 126.0, 126.8, 127.5, 128.2, 129.7, 130.3, 132.0, 133.5 (2×Ph), 172.6, 174.2 (2×C=O), 192.2 (C=S). Mass (*m/z*): 325 ($M^+$). Anal. Calcd for $C_{17}H_{15}N_3O_2S$: C, 62.75; H, 4.65; N, 12.91%. Found: C, 63.12; H, 4.41; N, 12.68%.

#### 4.2.3. Compound ***6c***

Yellowish needles (0.68 g, 88%), mp 138–139 °C. $[\alpha]_D^{20}$ −51.1 (*c* 0.5, MeOH), $t_R$=9.08 min. IR (KBr) $\nu_{max}$ 3352, 3309, 3050, 1741, 1704, 1685, 1603, 1579, 1452 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$+$D_2O$/TMS) $\delta$: 5.02 (d, 1H, $J$=9.2 Hz, H-6), 5.75 (d, 1H, $J$=9.2 Hz, H-5), 7.45–7.85 (m, $15H_{arom}$). $^{13}C$ NMR (DMSO-$d_6$/TMS) $\delta$: 61.0 (5-C), 62.7 (6-C), 126.3, 127.0, 127.6, 128.3, 129.0, 129.6, 130.7, 131.4, 132.0, 132.7, 133.4, 134.1 (3×Ph), 172.2, 173.1, 174.2 (3×C=O). Mass (*m/z*): 385 ($M^+$). Anal. Calcd for $C_{23}H_{19}N_3O_3$: C, 71.67; H, 4.97; N, 10.90%. Found: C, 71.92; H, 5.23; N, 10.54%.

#### 4.2.4. Compound ***6d***

Yellowish needles (0.64 g, 80%), mp 145–147 °C. $[\alpha]_D^{20}$ −71.3 (*c* 0.5, MeOH), $t_R$=8.72 min. IR (KBr) $\nu_{max}$ 3348, 3313, 3051, 1710, 1690, 1598, 1583, 1453, 1058 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$+$D_2O$/TMS) $\delta$: 5.05 (d, 1H, $J$=9.2 Hz, H-6), 5.68 (d, 1H, $J$=9.2 Hz, H-5), 7.20–7.93 (m, $15H_{arom}$). $^{13}C$ NMR (DMSO-$d_6$/TMS) $\delta$: 61.6 (5-C), 62.3 (6-C), 125.7, 126.4, 127.1, 128.0, 128.8, 129.4, 130.2, 130.8, 131.5, 132.3, 133.0, 133.9 (3×Ph), 173.1, 176.8 (2×C=O), 192.5 (C=S). Mass (*m/z*): 401 ($M^+$). Anal. Calcd for $C_{23}H_{19}N_3O_2S$: C, 68.81; H, 4.77; N, 10.47%. Found: C, 69.17; H, 4.48; N, 10.68%.

#### 4.2.5. Compound ***6e***

Yellowish needles (0.73 g, 92%), mp 134–135 °C. $[\alpha]_D^{20}$ −58.5 (*c* 0.5, MeOH), $t_R$=8.72 min. IR (KBr) $\nu_{max}$ 3355, 3309, 3055, 1737, 1711, 1688, 1602, 1585, 1451 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$+$D_2O$/TMS) $\delta$: 3.70 (s, 3H, Me), 5.01 (d, 1H, $J$=9.2 Hz, H-6), 5.71 (d, 1H, $J$=9.2 Hz, H-5), 7.11–7.78 (m, $14H_{arom}$). $^{13}C$ NMR (DMSO-$d_6$/TMS) $\delta$: 20.5 (Me), 61.9 (5-C), 63.1 (6-C), 125.7, 126.3, 127.1, 127.7, 128.4, 129.0, 129.6, 130.3, 131.0, 131.6, 132.5, 133.1, 133.8, 134.6 (2×Ph, 2-$MeC_6H_4$), 172.1, 173.5, 174.8 (3×C=O). Mass (*m/z*): 399 ($M^+$). Anal. Calcd for $C_{24}H_{21}N_3O_3$: C, 72.16; H, 5.30; N, 10.52%. Found: C, 71.79; H, 5.64; N, 10.39%.

#### 4.2.6. Compound ***6f***

Yellowish needles (0.57 g, 84%), mp 141–143 °C. $[\alpha]_D^{20}$ −49.8 (*c* 0.5, MeOH), $t_R$=8.83 min. IR (KBr) $\nu_{max}$ 3351, 3310, 3049, 1735, 1708, 1691, 1605, 1580, 1455 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$+$D_2O$/TMS) $\delta$: 1.12 (t, 3H, $J$=6.5 Hz), 2.61 (q, 2H, $J$=6.5 Hz), 5.07 (d, 1H, $J$=9.2 Hz, H-6), 5.69 (d, 1H, $J$=9.2 Hz, H-5), 7.23–7.91 (m, $10H_{arom}$). $^{13}C$ NMR (DMSO-$d_6$/TMS) $\delta$: 13.7 ($CH_2CH_3$), 58.2 ($CH_2CH_3$), 62.0 (5-C), 63.8 (6-C), 126.8, 128.2, 129.7, 130.6, 132.0, 132.8, 133.7, 134.6 (2×Ph), 172.5, 173.9, 174.8 (3×C=O). Mass (*m/z*): 337 ($M^+$). Anal. Calcd for $C_{19}H_{19}N_3O_3$: C, 64.64; H, 5.68; N, 12.46%. Found: C, 64.89; H, 5.53; N, 12.82%.

#### 4.2.7. Compound ***6g***

Yellowish needles (0.62 g, 90%), mp 119–120 °C. $[\alpha]_D^{20}$ −50.8 (*c* 0.5, MeOH), $t_R$=9.23 min. IR (KBr) $\nu_{max}$ 3348, 3309, 3048, 1738, 1708, 1680, 1599, 1588, 1456 $cm^{-1}$.

$^1$H NMR (DMSO-$d_6$+$D_2O$/TMS) $\delta$: 4.98 (d, 1H, $J$=9.2 Hz, H-6), 5.71 (d, 1H, $J$=9.2 Hz, H-5), 7.21–7.49 (m, 7H$_{arom}$), 7.57–7.98 (m, 2H$_{arom}$). $^{13}$C NMR (DMSO-$d_6$/TMS) $\delta$: 61.3 (5-C), 62.7 (6-C), 126.5, 127.2, 128.1, 128.8, 129.5, 130.2, 131.7, 132.9 (Ph, 4-Cl$C_6H_4$), 172.3, 173.1, 174.5 (3×C=O). Mass (*m*/*z*): 343, 345 ($M^+$, $M^+$+2). Anal. Calcd for $C_{17}H_{14}ClN_3O_3$: C, 59.40; H, 4.10; N, 12.22%. Found: C, 59.66; H, 4.03; N, 11.97%.

#### 4.2.8. Compound **6h**

Yellowish needles (0.62 g, 87%), mp 165–167 °C. $[\alpha]_D^{20}$ −69.5 (*c* 0.5, MeOH), $t_R$=8.79 min. IR (KBr) $\nu_{max}$ 3343, 3312, 3053, 1709, 1687, 1602, 1583, 1451, 1053 cm$^{-1}$. $^1$H NMR (DMSO-$d_6$+$D_2O$/TMS) $\delta$: 5.01 (d, 1H, $J$=9.2 Hz, H-6), 5.69 (d, 1H, $J$=9.2 Hz, H-5), 7.19–7.55 (m, 7H$_{arom}$), 7.61–7.93 (m, 2H$_{arom}$). $^{13}$C NMR (DMSO-$d_6$/TMS) $\delta$: 61.7 (5-C), 63.1 (6-C), 126.2, 127.9, 128.7, 129.5, 130.3, 131.2, 131.9, 133.2, 133.5 (Ph, 4-Cl$C_6H_4$), 172.5, 173.7 (2×C=O), 192.5 (C=S). Mass (*m*/*z*): 359, 361 ($M^+$, $M^+$+2). Anal. Calcd for $C_{17}H_{14}ClN_3O_2S$: C, 56.74; H, 3.92; N, 11.68%. Found: C, 56.59; H, 3.79; N, 11.91%.

### 4.3. Isolation of Michael adducts **5a**, **5c**, **5e** and **5g** and their conversion into the corresponding annulated products **6a**, **6c**, **6e** and **6g**

The procedure followed was the same as described above for the synthesis of **6** (Section 4.2) except that the time of stirring in this case was 10–15 h instead of 21–30 h for **6**. The adducts **5** were purified by silica gel column chromatography (hexane/EtOAc, 3:1) to obtain an analytically pure sample of **5** in 42–51% yield with 82–95% ee. The crude product was found to be a diastereomeric mixture containing 91–95% of the *anti* isomer as determined by $^1$H NMR spectroscopy. The adducts **5** were assigned the *anti* stereochemistry as their $^1$H NMR spectra exhibited higher values of coupling constant, $J_{cyclicNCH,acyclicNCH}$=9.5 Hz, than that of *syn* diastereomer, $J_{cyclicNCH,acyclicNCH}$=4.1 Hz.[33–39] A mixture of intermediate compound **5a**, **5c**, **5e** or **5g** (2.0 mmol) and L-prolinium sulfate (0.2 mmol) in 8 mL of THF was stirred at room temperature for 10–15 h to give the corresponding products **6a**, **6c**, **6e** or **6g** quantitatively. These were isolated and purified in the same way as described above in Section 4.2.

#### 4.3.1. Compound **5a**

Yellowish needles (0.32 g, 51%), mp 138–140 °C. $[\alpha]_D^{20}$ −50.9 (*c* 0.5, MeOH), $t_R$=8.59 min. IR (KBr) $\nu_{max}$ 3132, 3035, 1776, 1690, 1605, 1581, 1452, 1310 cm$^{-1}$. $^1$H NMR (DMSO-$d_6$+$D_2O$/TMS) $\delta$: 6.60 (d, 1H, $J$=9.5 Hz, acyclic NCH), 6.72 (d, 1H, $J$=9.5 Hz, cyclic NCH), 7.12–7.56 (m, 10H$_{arom}$). $^{13}$C NMR (DMSO-$d_6$/TMS) $\delta$: 60.5 (Ph–*C*), 63.5 (O=C–*C*), 126.5, 127.3, 129.0, 129.8, 130.5, 131.7, 132.5, 133.4 (2×Ph), 158.1 (C=N), 172.5, 173.2 (2×C=O). Mass (*m*/*z*): 309 ($M^+$). Anal. Calcd for $C_{17}H_{15}N_3O_3$: C, 66.01; H, 4.89; N, 13.58%. Found: C, 65.76; H, 4.78; N, 13.81%.

#### 4.3.2. Compound **5c**

Yellowish needles (0.35 g, 45%), mp 128–129 °C. $[\alpha]_D^{20}$ −43.2 (*c* 0.5, MeOH), $t_R$=8.71 min. IR (KBr) $\nu_{max}$ 3135, 3038, 1772, 1695, 1598, 1580, 1455, 1312 cm$^{-1}$. $^1$H NMR (DMSO-$d_6$+$D_2O$/TMS) $\delta$: 6.62 (d, 1H, $J$=9.5 Hz, acyclic NCH), 6.75 (d, 1H, $J$=9.5 Hz, cyclic NCH), 7.15–7.80 (m, 15H$_{arom}$). $^{13}$C NMR (DMSO-$d_6$/TMS) $\delta$: 60.3 (Ph–*C*), 63.7 (O=C–*C*), 126.1, 126.9, 127.6, 128.5, 129.2, 130.0, 130.7, 131.5, 132.1, 132.8, 133.5, 133.9 (3×Ph), 158.3 (C=N), 172.7, 173.8 (2×C=O). Mass (*m*/*z*): 385 ($M^+$). Anal. Calcd for $C_{23}H_{19}N_3O_3$: C, 71.67; H, 4.97; N, 10.90%. Found: C, 71.91; H, 4.61; N, 10.81%.

#### 4.3.3. Compound **5e**

Yellowish needles (0.34 g, 42%), mp 142–143 °C. $[\alpha]_D^{20}$ −47.2 (*c* 0.5, MeOH), $t_R$=8.63 min. IR (KBr) $\nu_{max}$ 3138, 3042, 1780, 1698, 1603, 1585, 1455, 1313 cm$^{-1}$. $^1$H (DMSO-$d_6$+$D_2O$/TMS) $\delta$: 2.28 (s, 3H, Me), 6.58 (d, 1H, $J$=9.5 Hz, acyclic NCH), 6.78 (d, 1H, $J$=9.5 Hz, cyclic NCH), 7.09–7.78 (m, 14H$_{arom}$). $^{13}$C NMR (DMSO-$d_6$/TMS) $\delta$: 20.3 (Me), 60.1 (Ph–*C*), 63.2 (O=C–*C*), 126.2, 127.0, 127.7, 128.3, 128.9, 129.4, 130.1, 130.8, 131.6, 132.3, 133.0, 133.7, 134.6, 135.3 (2×Ph, 2-Me$C_6H_4$), 158.0 (C=N), 172.3, 173.5 (2×C=O). Mass (*m*/*z*): 399 ($M^+$). Anal. Calcd for $C_{24}H_{21}N_3O_3$: C, 72.16; H, 5.30; N, 10.52%. Found: C, 72.41; H, 5.03; N, 10.78%.

#### 4.3.4. Compound **5g**

Yellowish needles (0.33 g, 48%), mp 133–135 °C. $[\alpha]_D^{20}$ −51.3 (*c* 0.5, MeOH), $t_R$=8.68 min. IR (KBr) $\nu_{max}$ 3133, 3038, 1781, 1696, 1605, 1585, 1449 cm$^{-1}$. $^1$H NMR (DMSO-$d_6$+$D_2O$/TMS) $\delta$: 6.65 (d, 1H, $J$=9.5 Hz, acyclic NCH), 6.73 (d, 1H, $J$=9.5 Hz, cyclic NCH), 7.09–7.48 (m, 7H$_{arom}$), 7.65–7.93 (m, 2H$_{arom}$). $^{13}$C NMR (DMSO-$d_6$/TMS) $\delta$: 60.4 (Ph–*C*), 63.8 (O=C–*C*), 126.3, 127.5, 128.9, 129.7, 130.7, 131.8, 132.6, 133.4 (Ph, 4-Cl$C_6H_4$), 158.5 (C=N), 172.3, 173.4 (2×C=O). Mass (*m*/*z*): 343, 345 ($M^+$, $M^+$+2). Anal. Calcd for $C_{17}H_{14}ClN_3O_3$: C, 59.40; H, 4.10; N, 12.22%. Found: C, 59.71; H, 4.33; N, 12.13%.

### 4.4. 5-Amino-6-phenyl-5,6-dihydropyrimidinedione analogues **7**: general procedure

Compound **6** (2.0 mmol) was refluxed in $H_2SO_4$/$H_2O$ (15 mL, 4:3, v/v) for 45 min in an oil bath. The reaction mixture was cooled, the desired product **7** was precipitated by adding concentrated $NH_4OH$ (specific gravity 0.88) under ice cooling and recrystallized from ethanol to obtain an analytically pure sample of **7**.

#### 4.4.1. Compound **7a**

Yellowish needles (0.36 g, 87%), mp 114–115 °C. $[\alpha]_D^{20}$ −43.9 (*c* 0.5, MeOH), $t_R$=8.35 min. IR (KBr) $\nu_{max}$ 3342, 3308, 3050, 1736, 1710, 1601, 1581, 1452 cm$^{-1}$. $^1$H NMR (DMSO-$d_6$+$D_2O$/TMS) $\delta$: 4.88 (d, 1H, $J$=9.2 Hz, H-6), 5.62 (d, 1H, $J$=9.2 Hz, H-5), 7.05–7.40 (m, 5H$_{arom}$). $^{13}$C NMR (DMSO-$d_6$/TMS) $\delta$: 61.8 (5-C), 64.2 (6-C), 127.5, 130.0,

133.0, 133.6 (Ph), 172.9, 173.8 (2×C=O). Mass (*m/z*): 205 ($M^+$). Anal. Calcd for $C_{10}H_{11}N_3O_2$: C, 58.53; H, 5.40; N, 20.48%. Found: C, 58.31; H, 5.68; N, 20.19%.

#### 4.4.2. Compound **7b**

Yellowish needles (0.41 g, 93%), mp 109–110 °C. $[\alpha]_D^{20}$ −61.8 (*c* 0.5, MeOH), $t_R$=8.05 min. IR (KBr) $\nu_{max}$ 3345, 3310, 3052, 1712, 1604, 1582, 1454, 1051 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$+$D_2O$/TMS) $\delta$: 4.79 (d, 1H, *J*=9.2 Hz, H-6), 5.58 (d, 1H, *J*=9.2 Hz, H-5), 7.13–7.43 (m, 5$H_{arom}$). $^{13}C$ NMR (DMSO-$d_6$/TMS) $\delta$: 61.6 (5-C), 64.5 (6-C), 126.8, 129.2, 131.9, 133.9 (Ph), 172.5 (C=O), 192.6 (C=S). Mass (*m/z*): 221 ($M^+$). Anal. Calcd for $C_{10}H_{11}N_3OS$: C, 54.28; H, 5.01; N, 18.99%. Found: C, 54.49; H, 5.32; N, 18.78%.

#### 4.4.3. Compound **7c**

Yellowish needles (0.51 g, 91%), mp 118–119 °C. $[\alpha]_D^{20}$ −45.5 (*c* 0.5, MeOH), $t_R$=8.31 min. IR (KBr) $\nu_{max}$ 3339, 3311, 3051, 1742, 1715, 1605, 1584, 1449 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$+$D_2O$/TMS) $\delta$: 4.80 (d, 1H, *J*=9.2 Hz, H-6), 5.61 (d, 1H, *J*=9.2 Hz, H-5), 7.31–7.68 (m, 10$H_{arom}$). $^{13}C$ NMR (DMSO-$d_6$/TMS) $\delta$: 61.5 (5-C), 64.9 (6-C), 126.2, 127.8, 128.8, 130.6, 131.4, 132.8, 133.9, 134.5 (2×Ph), 171.8, 173.5 (2×C=O). Mass (*m/z*): 281 ($M^+$). Anal. Calcd for $C_{16}H_{15}N_3O_2$: C, 68.31; H, 5.37; N, 14.94%. Found: C, 68.48; H, 5.23; N, 14.81%.

#### 4.4.4. Compound **7d**

Yellowish needles (0.52 g, 88%), mp 130–131 °C. $[\alpha]_D^{20}$ −67.5 (*c* 0.5, MeOH), $t_R$=8.12 min. IR (KBr) $\nu_{max}$ 3338, 3309, 3054, 1710, 1599, 1579, 1448, 1055 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$+$D_2O$/TMS) $\delta$: 4.82 (d, 1H, *J*=9.2 Hz, H-6), 5.58 (d, 1H, *J*=9.2 Hz, H-5), 7.17–7.79 (m, 10$H_{arom}$). $^{13}C$ NMR (DMSO-$d_6$/TMS) $\delta$: 61.3 (5-C), 64.7 (6-C), 127.2, 129.0, 130.8, 131.6, 132.5, 133.1, 133.8, 134.6 (2×Ph), 173.4 (C=O), 192.8 (C=S). Mass (*m/z*): 297 ($M^+$). Anal. Calcd for $C_{16}H_{15}N_3OS$: C, 64.62; H, 5.08; N, 14.13%. Found: C, 64.29; H, 5.34; N, 13.87%.

#### 4.4.5. Compound **7e**

Yellowish needles (0.55 g, 94%), mp 127–128 °C. $[\alpha]_D^{20}$ −47.2 (*c* 0.5, MeOH), $t_R$=8.41 min. IR (KBr) $\nu_{max}$ 3340, 3307, 3052, 1745, 1713, 1604, 1577, 1455 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$+$D_2O$/TMS) $\delta$: 3.65 (s, 3H, Me), 4.78 (d, 1H, *J*=9.2 Hz, H-6), 5.65 (d, 1H, *J*=9.2 Hz, H-5), 7.29–7.78 (m, 9$H_{arom}$). $^{13}C$ NMR (DMSO-$d_6$/TMS) $\delta$: 21.2 (Me), 61.9 (5-C), 64.8 (6-C), 126.2, 127.1, 127.9, 128.6, 129.3, 130.0, 130.8, 131.4, 132.5, 133.7 (2×Ph, 2-Me$C_6H_4$), 172.2, 174.8 (2×C=O). Mass (*m/z*): 295 ($M^+$). Anal. Calcd for $C_{17}H_{17}N_3O_2$: C, 69.14; H, 5.80; N, 14.23%. Found: C, 69.31; H, 5.58; N, 14.49%.

#### 4.4.6. Compound **7f**

Yellowish needles (0.43 g, 92%), mp 124–125 °C. $[\alpha]_D^{20}$ −53.5 (*c* 0.5, MeOH), $t_R$=8.27 min. IR (KBr) $\nu_{max}$ 3341, 3310, 3055, 1742, 1715, 1605, 1585, 1452 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$+$D_2O$/TMS) $\delta$: 1.15 (t, 3H, *J*=6.5 Hz), 2.59 (q, 2H, *J*=6.5 Hz), 4.85 (d, 1H, *J*=9.2 Hz, H-6), 5.63 (d, 1H, *J*=9.2 Hz, H-5), 7.45–7.93 (m, 5$H_{arom}$). $^{13}C$ NMR (DMSO-$d_6$/TMS) $\delta$: 13.3 ($CH_2CH_3$), 57.9 ($CH_2CH_3$), 61.3 (5-C), 64.5 (6-C), 126.2, 128.6, 130.5, 133.8 (Ph), 172.5, 174.7 (2×C=O). Mass (*m/z*): 233 ($M^+$). Anal. Calcd for $C_{12}H_{15}N_3O_2$: C, 61.79; H, 6.48; N, 18.01%. Found: C, 61.48; H, 6.29; N, 17.83%.

#### 4.4.7. Compound **7g**

Yellowish needles (0.44 g, 93%), mp 135–137 °C. $[\alpha]_D^{20}$ −58.2 (*c* 0.5, MeOH), $t_R$=8.38 min. IR (KBr) $\nu_{max}$ 3342, 3308, 3051, 1735, 1709, 1599, 1583, 1455 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$+$D_2O$/TMS) $\delta$: 4.91 (d, 1H, *J*=9.2 Hz, H-6), 5.65 (d, 1H, *J*=9.2 Hz, H-5), 7.09–7.39 (m, 2$H_{arom}$), 7.51–7.87 (m, 2$H_{arom}$). $^{13}C$ NMR (DMSO-$d_6$/TMS) $\delta$: 61.9 (5-C), 64.5 (6-C), 127.3, 128.5, 130.3, 132.8 (4-Cl$C_6H_4$), 172.7, 173.6 (2×C=O). Mass (*m/z*): 239, 241 ($M^+$, $M^+$+2). Anal. Calcd for $C_{10}H_{10}ClN_3O_2$: C, 50.12; H, 4.21; N, 17.53%. Found: C, 50.03; H, 4.48; N, 17.21%.

#### 4.4.8. Compound **7h**

Yellowish needles (0.46 g, 90%), mp 99–101 °C. $[\alpha]_D^{20}$ −69.8 (*c* 0.5, MeOH), $t_R$=8.17 min. IR (KBr) $\nu_{max}$ 3339, 3311, 3049, 1715, 1605, 1581, 1455, 1052 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$+$D_2O$/TMS) $\delta$: 4.76 (d, 1H, *J*=9.2 Hz, H-6), 5.59 (d, 1H, *J*=9.2 Hz, H-5), 7.12–7.47 (m, 2$H_{arom}$), 7.58–7.91 (m, 2$H_{arom}$). $^{13}C$ NMR (DMSO-$d_6$/TMS) $\delta$: 61.3 (5-C), 64.7 (6-C), 127.5, 128.8, 130.9, 132.7 (4-Cl$C_6H_4$), 172.9 (C=O), 193.1 (C=S). Mass (*m/z*): 255, 257 ($M^+$, $M^+$+2). Anal. Calcd for $C_{10}H_{10}ClN_3OS$: C, 46.97; H, 3.94; N, 16.43%. Found: C, 47.13; H, 4.23; N, 16.51%.

### 4.5. 5-Mercapto-6-phenylperhydropyrimidines **10**: general procedure

The procedure followed was the same as described above for the synthesis of **6** except that the active methylene component in this case was 2-methyl-2-phenyl-1,3-oxathiolan-5-one **8** instead of 2-phenyl-1,3-oxazol-5-one **4**. To obtain analytically pure sample of a single diastereomer **10** (82–93% yield and 78–95% ee) and to assign the stereochemistry, the same procedure was adopted as described for **6**. The crude product in this case was found to be a diastereomeric mixture containing 92–97% of the trans isomer as determined by $^1H$ NMR spectroscopy.

#### 4.5.1. Compound **10a**

Yellowish needles (0.39 g, 87%), mp 97–99 °C. $[\alpha]_D^{20}$ −51.3 (*c* 0.5, MeOH), $t_R$=8.62 min. IR (KBr) $\nu_{max}$ 3350, 3052, 2550, 1741, 1712, 1602, 1582, 1454 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$+$D_2O$/TMS) $\delta$: 5.83 (d, 1H, *J*=9.2 Hz, H-6), 6.10 (d, 1H, *J*=9.2 Hz, H-5), 7.11–7.39 (m, 5$H_{arom}$). $^{13}C$ NMR (DMSO-$d_6$/TMS) $\delta$: 26.5 (5-C), 43.3 (6-C), 128.8, 131.2, 132.5, 133.8 (Ph), 166.8, 170.5 (2×C=O). Mass (*m/z*): 226 ($M^+$). Anal. Calcd for $C_{10}H_{10}N_2O_2S$: C, 54.04; H, 4.53; N, 12.60%. Found: C, 54.29; H, 4.31; N, 12.45%.

#### 4.5.2. Compound **10b**

Yellowish needles (0.43 g, 90%), mp 90–92 °C. $[\alpha]_D^{20}$ −68.9 (*c* 0.5, MeOH), $t_R$=8.29 min. IR (KBr) $\nu_{max}$ 3349,

3055, 2556, 1715, 1605, 1585, 1452, 1052 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$+$D_2O$/TMS) $\delta$: 5.80 (d, 1H, $J$=9.2 Hz, H-6), 6.13 (d, 1H, $J$=9.2 Hz, H-5), 7.21–7.98 (m, $5H_{arom}$). $^{13}C$ NMR (DMSO-$d_6$/TMS) $\delta$: 26.9 (5-C), 44.0 (6-C), 127.5, 128.9, 132.8, 134.0 (Ph), 166.5 (C=O), 192.8 (C=S). Mass (*m/z*): 238 ($M^+$). Anal. Calcd for $C_{10}H_{10}N_2OS_2$: C, 50.40; H, 4.23; N, 11.75%. Found: C, 50.71; H, 4.09; N, 11.92%.

#### 4.5.3. Compound **10c**

Yellowish needles (0.49 g, 82%), mp 105–106 °C. $[\alpha]_D^{20}$ −57.2 (*c* 0.5, MeOH), $t_R$=8.38 min. IR (KBr) $\nu_{max}$ 3352, 3048, 2560, 1745, 1710, 1598, 1579, 1450 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$+$D_2O$/TMS) $\delta$: 5.85 (d, 1H, $J$=9.2 Hz, H-6), 6.06 (d, 1H, $J$=9.2 Hz, H-5), 7.15–8.02 (m, $10H_{arom}$). $^{13}C$ NMR (DMSO-$d_6$/TMS) $\delta$: 27.2 (5-C), 44.5 (6-C), 126.5, 127.3, 128.2, 129.7, 130.5, 131.7, 132.4, 133.5 (2×Ph), 167.1, 171.2 (2×C=O). Mass (*m/z*): 298 ($M^+$). Anal. Calcd for $C_{16}H_{14}N_2O_2S$: C, 64.41; H, 4.73; N, 9.39%. Found: C, 64.58; H, 4.41; N, 9.18%.

#### 4.5.4. Compound **10d**

Yellowish needles (0.53 g, 85%), mp 127–129 °C. $[\alpha]_D^{20}$ −57.8 (*c* 0.5, MeOH), $t_R$=8.33 min. IR (KBr) $\nu_{max}$ 3355, 3047, 2558, 1709, 1596, 1577, 1452, 1056 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$+$D_2O$/TMS) $\delta$: 5.80 (d, 1H, $J$=9.2 Hz, H-6), 6.17 (d, 1H, $J$=9.2 Hz, H-5), 7.06–7.59 (m, $10H_{arom}$). $^{13}C$ NMR (DMSO-$d_6$/TMS) $\delta$: 26.7 (5-C), 43.5 (6-C), 127.0, 127.9, 128.6, 129.5, 130.3, 131.1, 132.2, 132.9 (2×Ph), 173.4 (C=O), 192.8 (C=S). Mass (*m/z*): 314 ($M^+$). Anal. Calcd for $C_{16}H_{14}N_2OS_2$: C, 61.12; H, 4.49; N, 8.91%. Found: C, 60.85; H, 4.75; N, 8.99%.

#### 4.5.5. Compound **10e**

Yellowish needles (0.58 g, 93%), mp 164–165 °C. $[\alpha]_D^{20}$ −49.8 (*c* 0.5, MeOH), $t_R$=8.45 min. IR (KBr) $\nu_{max}$ 3352, 3050, 2562, 1742, 1713, 1603, 1581, 1455 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$+$D_2O$/TMS) $\delta$: 3.72 (s, 3H, Me), 5.88 (d, 1H, $J$=9.2 Hz, H-6), 6.12 (d, 1H, $J$=9.2 Hz, H-5), 7.09–8.23 (m, $9H_{arom}$). $^{13}C$ NMR (DMSO-$d_6$/TMS) $\delta$: 20.8 (Me), 27.7 (5-C), 43.2 (6-C), 126.2, 127.0, 127.8, 128.6, 129.3, 130.1, 130.7, 131.3, 132.0, 133.8 (2×Ph, 2-$MeC_6H_4$), 166.7, 171.5 (2×C=O). Mass (*m/z*): 312 ($M^+$). Anal. Calcd for $C_{17}H_{16}N_2O_2S$: C, 65.36; H, 5.16; N, 8.97%. Found: C, 65.09; H, 5.42; N, 9.25%.

#### 4.5.6. Compound **10f**

Yellowish needles (0.42 g, 83%), mp 134–135 °C. $[\alpha]_D^{20}$ −48.3 (*c* 0.5, MeOH), $t_R$=8.71 min. IR (KBr) $\nu_{max}$ 3348, 3051, 2565, 1745, 1710, 1601, 1582, 1454 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$+$D_2O$/TMS) $\delta$: 1.17 (t, 3H, $J$=6.5 Hz), 2.57 (q, 2H, $J$=6.5 Hz), 5.85 (d, 1H, $J$=9.2 Hz, H-6), 6.13 (d, 1H, $J$=9.2 Hz, H-5), 7.12–8.17 (m, $5H_{arom}$). $^{13}C$ NMR (DMSO-$d_6$/TMS) $\delta$: 13.8 ($CH_2CH_3$), 58.4 ($CH_2CH_3$), 26.8 (5-C), 43.6 (6-C), 126.8, 129.2, 131.4, 132.6 (Ph), 172.5, 174.7 (2×C=O). Mass (*m/z*): 250 ($M^+$). Anal. Calcd for $C_{12}H_{14}N_2O_2S$: C, 57.58; H, 5.64; N, 11.19%. Found: C, 57.86; H, 5.87; N, 10.83%.

#### 4.5.7. Compound **10g**

Yellowish needles (0.45 g, 88%), mp 112–113 °C. $[\alpha]_D^{20}$ −45.7 (*c* 0.5, MeOH), $t_R$=8.75 min. IR (KBr) $\nu_{max}$ 3351, 3055, 2552, 1748, 1711, 1605, 1583, 1455 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$+$D_2O$/TMS) $\delta$: 5.85 (d, 1H, $J$=9.2 Hz, H-6), 6.09 (d, 1H, $J$=9.2 Hz, H-5), 7.13–7.46 (m, $2H_{arom}$), 7.58–7.89 (m, $2H_{arom}$). $^{13}C$ NMR (DMSO-$d_6$/TMS) $\delta$: 26.7 (5-C), 43.2 (6-C), 127.3, 129.5, 131.3, 133.5 (4-$ClC_6H_4$), 166.7, 170.8 (2×C=O). Mass (*m/z*): 256, 258 ($M^+$, $M^+$+2). Anal. Calcd for $C_{10}H_9ClN_2O_2S$: C, 46.79; H, 3.53; N, 10.91%. Found: C, 46.68; H, 3.69; N, 11.03%.

#### 4.5.8. Compound **10h**

Yellowish needles (0.50 g, 91%), mp 139–141 °C. $[\alpha]_D^{20}$ −65.3 (*c* 0.5, MeOH), $t_R$=8.31 min. IR (KBr) $\nu_{max}$ 3348, 3053, 2556, 1709, 1602, 1587, 1451, 1057 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$+$D_2O$/TMS) $\delta$: 5.80 (d, 1H, $J$=9.2 Hz, H-6), 6.13 (d, 1H, $J$=9.2 Hz, H-5), 7.21–7.98 (m, $5H_{arom}$). $^{13}C$ NMR (DMSO-$d_6$/TMS) $\delta$: 26.9 (5-C), 44.0 (6-C), 127.5, 128.9, 132.8, 134.0 (Ph), 166.5 (C=O), 192.8 (C=S). Mass (*m/z*): 272, 274 ($M^+$, $M^+$+2). Anal. Calcd for $C_{10}H_9ClN_2OS_2$: C, 44.03; H, 3.33; N, 10.27%. Found: C, 44.39; H, 3.45; N, 10.18%.

### 4.6. Isolation of Michael adducts **9a**, **9c**, **9e** and **9g** and their conversion into the corresponding annulated products **10a**, **10c**, **10e** and **10g**

The procedure followed was the same as described above for the isolation of **5** (Section 4.3). Thus, analytically pure samples of **9a**, **9c**, **9e** and **9g** were obtained in 44–52% yield with 83–94% ee. The stereochemistry was assigned in the same way as described for **5**. The crude product in this case was found to be a diastereomeric mixture containing 92–97% of the *anti* isomer. The compounds **9a**, **9c**, **9e** and **9g** were converted into the corresponding annulated products **10a**, **10c**, **10e** and **10g** quantitatively, in the same way as described above in Section 4.3.

#### 4.6.1. Compound **9a**

Yellowish needles (0.34 g, 49%), mp 109–110 °C. $[\alpha]_D^{20}$ −51.8 (*c* 0.5, MeOH), $t_R$=8.23 min. IR (KBr) $\nu_{max}$ 3138, 3036, 1781, 1688, 1598, 1585, 1455 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$+$D_2O$/TMS) $\delta$: 2.33 (s, 3H, Me), 4.92 (d, 1H, $J$=9.5 Hz, SCH), 5.98 (d, 1H, $J$=9.5 Hz, NCH), 7.21–7.87 (m, $10H_{arom}$). $^{13}C$ NMR (DMSO-$d_6$/TMS) $\delta$: 34.5 (Ph–*C*–Me), 64.2 (Ph–*C*), 68.5 (O=C–*C*), 127.0, 127.7, 128.9, 129.8, 130.6, 131.4, 132.0, 133.6 (2×Ph), 171.9, 172.8 (2×C=O). Mass (*m/z*): 342 ($M^+$). Anal. Calcd for $C_{18}H_{18}N_2O_3S$: C, 63.14; H, 5.30; N, 8.18%. Found: C, 63.39; H, 5.47; N, 7.78%.

#### 4.6.2. Compound **9c**

Yellowish needles (0.43 g, 52%), mp 118–120 °C. $[\alpha]_D^{20}$ −47.2 (*c* 0.5, MeOH), $t_R$=8.17 min. IR (KBr) $\nu_{max}$ 3140, 3039, 1779, 1692, 1600, 1581, 1451 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$+$D_2O$/TMS) $\delta$: 2.35 (s, 3H, Me), 4.95 (d, 1H, $J$=9.5 Hz, SCH), 5.96 (d, 1H, $J$=9.5 Hz, NCH), 7.35–7.92 (m, $15H_{arom}$). $^{13}C$ NMR (DMSO-$d_6$/TMS) $\delta$: 34.7 (Ph–*C*–

Me), 64.5 (Ph–*C*), 68.2 (O=C–*C*), 126.0, 126.6, 127.3, 128.0, 128.6, 129.6, 130.4, 131.0, 131.7, 132.3, 133.0, 133.8 (3×Ph), 172.3, 173.2 (2×C=O). Mass (*m*/*z*): 418 ($M^+$). Anal. Calcd for $C_{24}H_{22}N_2O_3S$: C, 68.88; H, 5.30; N, 6.69%. Found: C, 68.57; H, 5.45; N, 6.33%.

### 4.6.3. Compound **9e**

Yellowish needles (0.38 g, 44%), mp 149–152 °C. $[\alpha]_D^{20}$ −43.5 (*c* 0.5, MeOH), $t_R$=8.31 min. IR (KBr) $\nu_{max}$ 3136, 3033, 1785, 1690, 1604, 1578, 1453 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$+$D_2O$/TMS) $\delta$: 2.31 (s, 6H, 2×Me), 4.89 (d, 1H, *J*=9.5 Hz, SCH), 6.02 (d, 1H, *J*=9.5 Hz, NCH), 7.31–7.85 (m, 14$H_{arom}$). $^{13}C$ NMR (DMSO-$d_6$/TMS) $\delta$: 20.1 (Me), 34.7 (Ph–*C*–Me), 64.1 (Ph–*C*), 68.9 (O=C–*C*), 126.2, 126.9, 127.5, 128.1, 128.7, 129.4, 130.0, 130.6, 131.3, 132.0, 132.6, 133.2, 133.8, 134.5 (2×Ph, 2-Me$C_6H_4$), 172.5, 173.5 (2×C=O). Mass (*m*/*z*): 432 ($M^+$). Anal. Calcd for $C_{25}H_{24}N_2O_3S$: C, 69.42; H, 5.59; N, 6.48%. Found: C, 69.65; H, 5.34; N, 6.68%.

### 4.6.4. Compound **9g**

Yellowish needles (0.38 g, 51%), mp 127–129 °C. $[\alpha]_D^{20}$ −45.2 (*c* 0.5, MeOH), $t_R$=8.28 min. IR (KBr) $\nu_{max}$ 3135, 3038, 1782, 1689, 1605, 1585, 1448 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$+$D_2O$/TMS) $\delta$: 2.34 (s, 3H, Me), 4.93 (d, 1H, *J*=9.5 Hz, SCH), 5.96 (d, 1H, *J*=9.5 Hz, NCH), 7.11–7.53 (m, 7$H_{arom}$), 7.68–7.98 (m, 2$H_{arom}$). $^{13}C$ NMR (DMSO-$d_6$/TMS) $\delta$: 34.4 (Ph–*C*–Me), 64.5 (Ph–*C*), 68.7 (O=C–*C*), 126.7, 127.3, 128.2, 129.1, 129.9, 130.8, 131.7, 132.8 (Ph, 4-$ClC_6H_4$), 171.8, 172.6 (2×C=O). Mass (*m*/*z*): 376, 378 ($M^+$, $M^+$+2). Anal. Calcd for $C_{18}H_{17}ClN_2O_3S$: C, 57.37; H, 4.55; N, 7.43%. Found: C, 57.23; H, 4.76; N, 7.71%.

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