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L-Proline-catalysed three-component domino reactions for the diastereoselective synthesis of 5,6-disubstituted 3-thiomorpholinones

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ABSTRACT

L-Proline-catalysed three-component domino reactions of ethyl 2-[(2-oxo-2-arylethyl)sulfanyl]acetate, aromatic aldehydes and ammonia provide a rapid and facile access to novel *trans*-6-aroyl-5-aryl-3-thiomorpholinones. This diastereoselective reaction presumably proceeds via a domino sequence comprising enamine formation, Mannich reaction and intramolecular amidation individual steps and resulting in the generation of one C–C and two C–N bonds in a one-pot operation. The reaction also creates two contiguous stereocenters with complete diastereoselectivity.

1. Introduction

Compounds containing the 3-thiomorpholinone skeleton show interesting biological activities, such as enhancement of brain noradrenaline and dopamine turnover,[1] hypnotic activity[2] and antagonism on 5-HT1b[3] and EP4 receptors,[4] among others. This nucleus is also present in pharmacologically relevant fused systems, such as the 1,4-benzothiazine calcium antagonist semotiadil,[5] as well as in a pyrimido[1,4]thiazine derivative designed as an inhibitor of the glycinamide ribonucleotide transformylase with potent cell growth inhibition.[6] Hence, the 3-thiomorpholinone skeleton has emerged as an attractive template for the construction of chemical libraries for high-throughput screening aimed at the generation of new bioactive compounds. However, only a few methods have been described in the literature for the construction of thiomorpholinones since the synthesis of the parent thiomorpholin-3-one was first reported by Bestian.[7] Other methods for the preparation of this type of derivatives include: (i) a base-promoted reaction of 2-oxazolidinones with thiols,[8] (ii) a regiospecific nucleophilic displacement of 1,2-cyclic sulfamidates with methyl thioglycolate,[9] (iii) a traceless solid phase synthesis[10] involving several steps and expensive reagents, (iv) the intramolecular Ugi-four component synthesis described by Marcaccini et al.[11] and (v) syntheses employing glycidic esters,[12] thiazolidines[13] and 2-aminoethanethiol.[14]

The biological importance of 3-thiomorpholinones, in conjunction with our interest in developing novel domino processes,[15] led us to investigate the synthesis of compounds **3** employing L-proline as catalyst. Domino reactions,[16] being one-pot multi-step processes, obviate the isolation and purification of intermediates and hence provide expedient access to complex molecules thus rendering the synthetic protocols convergent and efficient. Our choice of proline, which has been described as 'the smallest enzyme',[17] was prompted by the fact that it is an abundant and inexpensive catalyst capable of triggering diverse organic transformations, in both enantio- and non-enantioselective fashions, including aldol,[18] Mannich,[19] Michael,[20] Biginelli[21] and Diels–Alder/Knoevenagel[22] reactions, together with more complex domino sequences.[23] Proline can play multiple catalytic roles; because it contains carboxylic acid and amine functionalities, it can act as either an acid, a base or both simultaneously, form enamines or iminium species with carbonyl compounds and can also facilitate orchestrated chemical transformations, similar to enzymatic catalysis.[24]

2. Results and discussion

We describe in this paper the L-proline-catalysed three-component domino reactions of ethyl 2-[(2-oxo-2-arylethyl)sulfanyl] acetates **1**, aromatic aldehydes **2** and ammonia to give *trans*-6-aroyl-5-aryl-3-thiomorpholinones **3** in diastereoselective fashion

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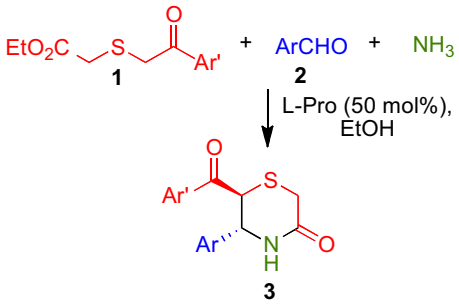
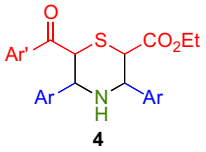
(Scheme 1). The starting materials for our study (compounds **1**) were prepared by the reaction of phenacyl bromides and ethyl 2-mercaptoacetate in the presence of potassium carbonate in chloroform, in an average 95% yield. In contrast, the preparation of **1** had been reported earlier in 55–68% yield from the same starting materials in the presence of sodium hydroxide in methanol.[25]



Scheme 1. Three-component synthesis of thiomorpholinones.

It is pertinent to note that a similar reaction in the absence of proline has been previously studied,[25] but it resulted in the formation of different reaction products, namely compounds **4**, which were isolated in unspecified stereochemistry. Therefore, our work illustrates how the use of L-proline as a catalyst provides a subtle way of altering the product selectivity of certain organic reactions.



Initially, a representative reaction affording **3a** was investigated in the presence of different bases. The data in Table 1 show that L-proline catalyzes the reaction more efficiently than pyrrolidine (entries 1 and 2). In the presence of DMAP and DBU, the reaction affords slightly lower yields. The pK_a values of conjugate acids of these bases reveal that their basicity varies in the order: DMAP>pyrrolidine>proline>DBU,[26] which indicates that probably catalysis by different mechanisms, viz. via intermediacy of enolates in the case of DMAP and DBU and enamines in the case of pyrrolidine and proline, are involved in this reaction. Between L-proline and pyrrolidine, the significantly enhanced yield of the product in proline-catalysed reaction suggests the involvement of carboxyl group as well in one or more steps of the domino reactions (vide infra). The reaction was found to proceed more efficiently in protic solvents (ethanol and methanol, entries 1 and 5) than in aprotic ones (DMF, DMSO, CH_3CN and THF, entries 6–9) suggesting the participation of polar transition states and intermediates in the domino reactions. Due to the slightly higher yield and its lower toxicity, we chose ethanol for our subsequent studies.

We then applied the optimal conditions to the synthesis of a library of compounds **3**. The reactions were performed by gently warming an ethanol solution containing equimolecular amounts of the starting materials and leaving the reaction mixture at ambient temperature for 12 h, which afforded stereoselectively the *trans*-6-aroyl-5-aryl-3-thiomorpholinones **3a–l** in 42–71% yields (Scheme 1 and Table 2). Chiral HPLC analysis of thiomorpholinone **3a** shows that it is almost racemic, the enantiomeric ratio being 49.84:50.16, and hence that the reaction occurs essentially in a non-enantioselective fashion.

Table 1
Catalyst and solvent optimization

Entry	Catalyst[a]	Solvent	Yield of **3a** (%)
1	L-Proline	Ethanol	65
2	Pyrrolidine	Ethanol	50
3	DMAP	Ethanol	48
4	DBU	Ethanol	42
5	L-Proline	Methanol	63
6	L-Proline	DMF	50
7	L-Proline	DMSO	49
8	L-Proline	CH_3CN	52
9	L-Proline	THF	45

[a] 50% of catalyst was employed in all cases.

Table 2
Scope and yields found in the synthesis of 3-thiomorpholinones **3**

Entry	Compound	Ar	Ar′	Yield (%)
1	**3a**	C_6H_5	C_6H_5	65
2	**3b**	4-FC_6H_4	C_6H_5	63
3	**3c**	4-ClC_6H_4	C_6H_5	56
4	**3d**	4-$H_3CC_6H_4$	C_6H_5	48
5	**3e**	4-$H_3COC_6H_4$	C_6H_5	42
6	**3f**	4-BrC_6H_4	C_6H_5	71
7	**3g**	2-FC_6H_4	C_6H_5	68
8	**3h**	2,4-$Cl_2C_6H_3$	C_6H_5	65
9	**3i**	4-$O_2NC_6H_4$	C_6H_5	44
10	**3j**	4-$H_3CC_6H_4$	4-ClC_6H_4	55
11	**3k**	4-ClC_6H_4	4-ClC_6H_4	52
12	**3l**	C_6H_5	4-$H_3CC_6H_4$	43

The structure of thiomorpholinones **3** was deduced from one- and two-dimensional NMR spectroscopic data as detailed for **3a** as a representative example (Fig. 1). The ^{1}H NMR spectrum of **3a** has two doublets at 3.26 and 3.41 ppm (J=16.5 Hz) due to the diastereotopic 2-CH_2 hydrogens and a doublet at 4.58 ppm (J=5.7 Hz) for H-6. The H-5 appears as a doublet of doublets at 5.26 ppm with J=5.7 and 2.7 Hz corresponding to the vicinal couplings with H-6 and NH at 4.58 and 6.07 ppm, respectively. These assignments are also supported by the HMBC correlations of H-6. The aromatic hydrogens give a multiplet at 7.33–7.87 ppm.

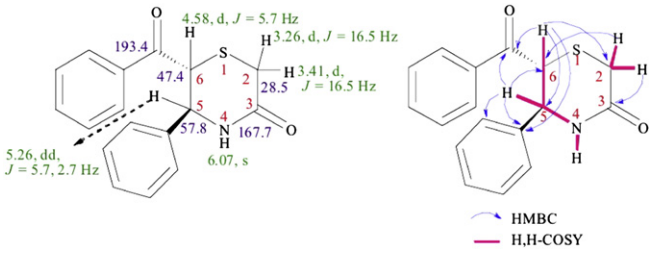


Fig. 1. ^{1}H and ^{13}C NMR chemical shifts and HMBCs of **3a**.

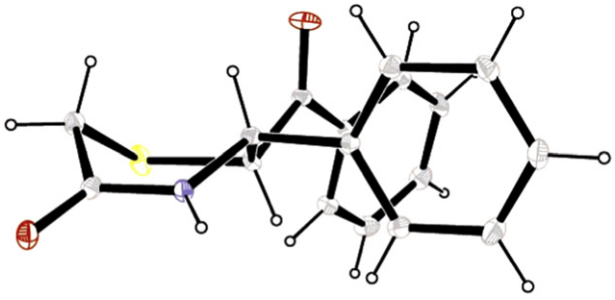
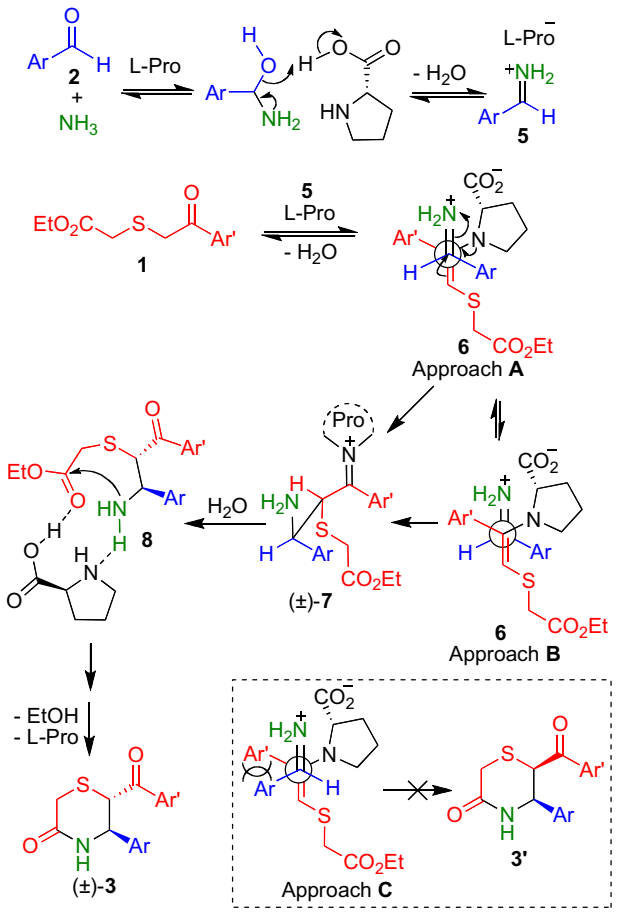


Fig. 2. ORTEP diagram of **3a**.

The X-ray study of a single crystal of **3a** confirmed the structure assigned from NMR spectroscopic data (Fig. 2). These studies show that the thiomorpholinone ring adopts a boat form, which is presumably imposed by the planarity of the amide function, resulting in allylic strain of the equatorial phenyl group with the amide NH hydrogen. This could lead to the phenyl group preferring an axial orientation, but this, in turn, would place the adjacent aroyl substituent, being in trans relationship with the former, in axial orientation with a concomitant 1,3-*syn* axial interaction with the axial proton. Hence, the system prefers a boat conformation, which is devoid of significant eclipsing interactions.

A plausible mechanism for the formation of thiomorpholinones **3** in the presence of L-proline is depicted in Scheme 2. Ethyl 2-[(2-oxo-2-arylethyl)sulfanyl]acetate **1** reacts with L-proline furnishing the enamine **6**, which reacts with iminium ion **5** to afford **7**. The approach of **5** to **6** occurs in the transition state with their two aryl rings away from each other, via approaches **A** or **B**, affording the *trans* thiomorpholinones. The approach depicted by **C** is presumably hampered by the steric interactions between the aryl rings, which explains the non-isolation of the *cis* diastereomers of **3**, viz. **3′**. Apparently, in the Mannich reaction between **5** and **6**, the carboxyl group does not catalyse the reaction, as any hydrogen bonding between the oxygen of the carboxyl group and the already positively charged iminium ion is bound to decrease the electrophilicity of the latter, which will diminish the reactivity. Hence the iminium ion **5** is able to react with **6** from both faces via **A** or **B**, ultimately giving racemic products. The significantly enhanced yield of the product in proline-catalysed reaction relative to that catalysed by pyrrolidine is in accord with the known multiple catalytic roles of L-proline as shown for the different steps of the domino reactions, namely (i) formation of imine/iminium ion and enamine and (ii) fast amidation via annulation affording **3** (Scheme 2). The latter reaction explains the absence of formation of the previously described products **4**, which requires an intermolecular reaction with aldehyde followed by an intramolecular Mannich reaction. Finally, the hydrolysis of the iminium group in **8** regenerates the molecule of L-proline initially consumed and results in the formation of thiomorpholinones **3**.



Scheme 2. Mechanistic proposal to explain the diastereoselective formation of compounds **3**.

3. Conclusion

In conclusion, the present study reports a unique one-pot, three-component diastereoselective synthesis of *trans*-6-aroyl-5-aryl-3-thiomorpholinones, structurally related to pharmaceutically relevant compounds, via a three-component reaction from ethyl 2-[(2-oxo-2-arylethyl)sulfanyl]acetate, aromatic aldehydes and ammonia in the presence of L-proline under mild reaction conditions. This novel transformation involves a domino process comprising enamine formation–Mannich reaction–annulation sequence and creates one carbon–carbon and two carbon–nitrogen bonds with complete regioselectivity. Furthermore, this transformation generates two adjacent stereocenters with complete selectivity. Finally, the synthetic process described here is attractive from an environmental point of view, as it requires only simple and readily available starting materials and an inexpensive and non-toxic catalyst (L-proline), and has water and ethanol as the only side products.

4. Experimental section

4.1. General experimental information

Melting points reported in this work are uncorrected. Flash column chromatography was performed on silica gel (230–400 mesh) using petroleum ether/ethyl acetate (24:1 v/v) as an eluent. The ^{1}H NMR, ^{13}C NMR, DEPT, H,H-COSY, C,H-COSY and HMBC spectra were recorded on a Bruker (Avance) 300 MHz instrument in $CDCl_3$ using TMS as an internal standard. Chemical shifts are given in parts per million (δ-scale) and the coupling constants are given in Hertz. Elemental analyses were performed on a Perkin–Elmer 2400 Series II Elemental CHN Analyser. IR spectra were recorded on an SHIMADZU FT IR instrument (KBr pellet in the case of solids and CH_2Cl_2 in the case of liquids). HPLC analysis was carried out on an SHIMADZU SCL-10A vp model with CHIRALCEL OD-H column using *n*-hexane/isopropyl alcohol [90:10 (v/v)] eluent at a flow rate of 0.5 mL/min.

4.2. Synthesis of thiomorpholinones 3. General procedure

A mixture of ethyl 2-[(2-oxo-2-arylethyl)sulfanyl]acetate (1 mmol), the suitable aromatic aldehyde (1 mmol), ammonia (1 mmol) and L-proline (50 mol %) in ethanol (10 mL) was gently warmed and kept at ambient temperature for 12 h. Then the reaction mixture was extracted with dichloromethane (20 mL), washed with water (3×20 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue thus obtained was chromatographed over silica gel (230–400 mesh) using petroleum ether/ethyl acetate (24:1 v/v) to afford pure thiomorpholinones **3**.

4.2.1. (±)-(5R,6S*)-6-Benzoyl-5-phenyl-3-thiomorpholinone (**3a**).* Isolated as pale yellow solid (0.163 g, 65%) mp=155 °C; ν_{max} (KBr) 3215, 1728, 1674 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 3.26 (1H, d, *J*=16.5 Hz, 2-C*H*$_2$), 3.41 (1H, d, *J*=16.5 Hz, 2-C*H*$_2$), 4.58 (1H, d,

J=5.7 Hz, 6-C*H*), 5.26 (1H, dd, *J*=5.7, 2.7 Hz, 5-C*H*), 6.07 (1H, s, N*H*), 7.33–7.87 (10H, m, Ar–H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 28.5, 47.4, 57.8, 127.2, 128.5, 128.7, 128.8, 129.0, 133.8, 134.6, 139.5, 167.7, 193.4. Anal. Calcd for $C_{17}H_{15}NO_2S$: C, 68.66; H, 5.08; N, 4.71. Found: C, 68.72; H, 5.04; N, 4.67. ee=0.4% determined by HPLC: CHIRALCEL OD-H column; *n*-hexane/isopropyl alcohol [90:10 (v/v)]; flow rate : 0.5 mL/min; λ=254 nm; t_R (major)=66.98 min; t_R (minor)= 94.12 min.

4.2.2. (±)-(5R,6S*)-6-Benzoyl-5-(4-fluorophenyl)-3-thiomorpholinone (**3b**).* Isolated as yellow solid (0.167 g, 63%) mp=167 °C; ν_{max} (KBr) 3235, 1714, 1652 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 3.26 (1H, d, *J*=16.5 Hz, 2-CH_2), 3.37 (1H, d, *J*=16.5 Hz, 2-CH_2), 4.46 (1H, d, *J*=5.4 Hz, 6-C*H*), 5.25 (1H, dd, *J*=5.4, 2.7 Hz, 5-C*H*), 6.32 (1H, s, N*H*), 7.05–7.85 (9H, m, Ar–H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 28.5, 47.4, 57.2, 115.9, 116.2, 129.0, 129.1, 129.2, 130.0, 132.8, 135.2, 140.5, 161.1, 167.4, 192.1. Anal. Calcd for $C_{17}H_{14}FNO_2S$: C, 64.75; H, 4.47; N, 4.44. Found: C, 64.67; H, 4.52; N, 4.50.

4.2.3. (±)-(5R,6S*)-6-Benzoyl-5-(4-chlorophenyl)-3-thiomorpholinone (**3c**).* Isolated as paste (0.156 g, 56%); ν_{max} (CH_2Cl_2) 3320, 1716, 1648 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 3.25 (1H, d, *J*=16.5 Hz, 2-CH_2), 3.43 (1H, d, *J*=16.5 Hz, 2-CH_2), 4.59 (1H, d, *J*=5.7 Hz, 6-C*H*), 5.28 (1H, dd, *J*=5.7, 2.7 Hz, 5-C*H*), 6.07 (1H, s, N*H*), 7.23–7.81 (9H, m, Ar–H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 28.8, 47.6, 57.8, 127.5, 128.3, 128.9, 129.3, 129.8, 134.2, 134.6, 140.2, 167.5, 192.8. Anal. Calcd for $C_{17}H_{14}ClNO_2S$: C, 61.53; H, 4.25; N, 4.22. Found: C, 61.59; H, 4.16; N, 4.17.

4.2.4. (±)-(5R,6S*)-6-Benzoyl-5-(4-methylphenyl)-3-thiomorpholinone (**3d**).* Isolated as paste (0.125 g, 48%); ν_{max} (CH_2Cl_2) 3240, 1720, 1680 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 2.34 (3H, s, CH_3), 3.28(1H, d, *J*=16.2 Hz, 2-CH_2), 3.48 (1H, d, *J*=16.2 Hz, 2-CH_2), 4.54 (1H, d, *J*=5.2 Hz, 6-C*H*), 5.21 (1H, dd, *J*=5.2, 2.5 Hz, 5-C*H*), 6.24 (1H, s, N*H*), 7.21–7.90 (9H, m, Ar–H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 21.3, 28.7, 47.7, 57.6, 127.7, 128.7, 129.1, 130.7, 131.6, 133.5, 136.1, 139.0, 167.8, 192.5. Anal. Calcd for $C_{18}H_{17}NO_2S$: C, 69.43; H, 5.50; N, 4.50. Found: C, 69.38; H, 5.58; N, 4.44.

4.2.5. (±)-(5R,6S*)-6-Benzoyl-5-(4-methoxyphenyl)-3-thiomorpholinone (**3e**).* Isolated as paste (0.116 g, 42%); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 3.25 (1H, d, *J*=16.4 Hz, 2-CH_2), 3.43 (1H, d, *J*=16.4 Hz, 2-CH_2), 3.72 (3H, s, OCH_3), 4.52 (1H, d, *J*=5.3 Hz, 6-C*H*), 5.24 (1H, dd, *J*=5.3, 2.7 Hz, 5-C*H*), 6.28 (1H, s, N*H*), 7.25–7.93 (9H, m, Ar–H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 28.3, 47.4, 55.3, 57.2, 114.1, 127.4, 128.9, 129.1, 130.1, 130.8, 133.7, 160.1, 167.5, 192.8. Anal. Calcd for $C_{18}H_{17}NO_3S$: C, 66.03; H, 5.23; N, 4.28. Found: C, 65.97; H, 5.19; N, 4.35.

4.2.6. (±)-(5R,6S*)-6-Benzoyl-5-(4-bromophenyl)-3-thiomorpholinone (**3f**).* Isolated as yellow solid (0.224 g, 71%) mp=198 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 3.26 (1H, d, *J*=16.5 Hz, 2-CH_2), 3.38 (1H, d, *J*=16.5 Hz, 2-CH_2), 4.50 (1H, d, *J*=5.3 Hz, 6-C*H*), 5.25 (1H, dd, *J*=5.3, 2.7 Hz, 5-C*H*), 6.31 (1H, s, N*H*), 7.28–7.89 (9H, m, Ar–H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 28.4, 47.1, 57.3, 122.8, 128.6, 128.8, 129.0, 132.1, 134.0, 134.3, 138.6, 167.6, 193.1. Anal. Calcd for $C_{17}H_{14}BrNO_2S$: C, 54.27; H, 3.75; N, 3.72. Found: C, 54.31; H, 3.69; N, 3.78.

4.2.7. (±)-(5R,6S*)-6-Benzoyl-5-(2-fluorophenyl)-3-thiomorpholinone (**3g**).* Isolated as yellow solid (0.180 g, 68%) mp=148 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 3.19 (1H, d, *J*=16.8 Hz, 2-CH_2), 3.33 (1H, d, *J*=16.8 Hz, 2-CH_2), 4.56 (1H, d, *J*=5.1 Hz, 6-C*H*), 5.56 (1H, dd, *J*=5.1, 2.6 Hz, 5-C*H*), 6.46 (1H, s, N*H*), 7.06–7.95 (9H, m, Ar–H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 27.7, 44.7, 51.8, 115.5, 115.8, 124.5, 126.9, 127.1, 128.6, 128.7, 129.5, 130.1, 130.2, 157.8, 161.1, 167.3, 193.1. Anal. Calcd for $C_{17}H_{14}FNO_2S$: C, 64.75; H, 4.47; N, 4.44. Found: C, 64.82; H, 4.52; N, 4.36.

4.2.8. (±)-(5R,6S*)-6-Benzoyl-5-(2,4-dichlorophenyl)-3-thiomorpholinone (**3h**).* Isolated as yellow solid (0.200 g, 65%) mp=163 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 3.12 (1H, d, *J*=17.4 Hz, 2-CH_2), 3.22 (1H, d, *J*=17.4 Hz, 2-CH_2), 4.43 (1H, d, *J*=5.4 Hz, 6-C*H*), 5.58 (1H, dd, *J*=5.4, 2.6 Hz, 5-C*H*), 6.99 (1H, s, N*H*), 7.26–7.98 (8H, m, Ar–H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 26.9, 43.0, 54.0, 127.5, 128.6, 128.8, 129.6, 130.6, 132.2, 133.7, 133.8, 134.9, 136.2, 167.0, 192.8. Anal. Calcd for $C_{17}H_{13}Cl_2NO_2S$: C, 55.75; H, 3.58; N, 3.82. Found: C, 55.83; H, 3.64; N, 3.78.

4.2.9. (±)-(5R,6S*)-6-Benzoyl-5-(4-nitrophenyl)-3-thiomorpholinone (**3i**).* Isolated as paste (0.126 g, 44%); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 3.26 (1H, d, *J*=16.5 Hz, 2-CH_2), 3.39 (1H, d, *J*=16.5 Hz, 2-CH_2), 4.51 (1H, d, *J*=5.4 Hz, 6-C*H*), 5.23 (1H, dd, *J*=5.4, 2.5 Hz, 5-C*H*), 6.32 (1H, s, N*H*), 7.26–7.90 (9H, m, Ar–H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 28.5, 47.2, 57.4, 123.0, 128.7, 129.0, 129.1, 132.3, 134.1, 134.5, 140.2, 167.7, 193.3. Anal. Calcd for $C_{17}H_{14}N_2O_4S$: C, 59.64; H, 4.12; N, 8.18. Found: C, 59.70; H, 4.03; N, 8.23.

4.2.10. (±)-(5R,6S*)-6-(4-Chlorobenzoyl)-5-(4-methylphenyl)-3-thiomorpholinone (**3j**).* Isolated as yellow solid (0.139 g, 55%) mp=131 °C; ν_{max} (KBr) 3310, 1711, 1664 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 2.44 (3H, s, CH_3), 3.27 (1H, d, *J*=16.2 Hz, 2-CH_2), 3.41 (1H, d, *J*=16.2 Hz, 2-CH_2), 4.52 (1H, d, *J*=5.9 Hz, 6-C*H*), 5.22 (1H, dd, *J*=5.9, 2.7 Hz, 5-C*H*), 6.01 (1H, s, N*H*), 7.44–7.78 (8H, m, Ar–H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 21.5, 28.7, 47.9, 57.9, 127.1, 127.7, 129.5, 129.8, 129.9, 130.0, 130.9, 143.6, 167.2, 192.1. Anal. Calcd for $C_{18}H_{16}ClNO_2S$: C, 62.51; H, 4.66; N, 4.05 Found: C, 62.55; H, 4.59; N, 4.11.

4.2.11. (±)-(5R,6S*)-6-(4-Chlorobenzoyl)-5-(4-chlorophenyl)-3-thiomorpholinone (**3k**).* Isolated as yellow solid (0.140 g, 52%) mp=116 °C; ν_{max} (KBr) 3220, 1719, 1670 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 3.20 (1H, d, *J*=16.8 Hz, 2-CH_2), 3.30 (1H, d, *J*=16.8 Hz, 2-CH_2), 4.38 (1H, d, *J*=5.1 Hz, 6-C*H*), 5.18 (1H, dd, *J*=5.1, 2.4 Hz, 5-C*H*), 5.86 (1H, s, N*H*), 7.30–7.75 (8H, m, Ar–H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 28.9, 47.3, 57.4, 128.6, 129.0, 129.5, 130.7, 130.9, 131.6, 133.9, 136.0, 166.7, 191.0. Anal. Calcd for $C_{17}H_{13}Cl_2NO_2S$: C, 55.75; H, 3.58; N, 3.82. Found: C, 55.82; H, 3.52; N, 3.86.

4.2.12. (±)-(5R,6S*)-6-(4-Methylbenzoyl)-5-phenyl-3-thiomorpholinone (**3l**).* Isolated as a viscous oil (0.105 g, 43%); ν_{max} (CH_2Cl_2) 3190, 1730, 1640 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 2.20 (3H, s, CH_3), 3.22 (1H, d, *J*=16.4 Hz, 2-CH_2), 3.37 (1H, d, *J*=16.4 Hz, 2-CH_2), 4.55 (1H, d, *J*=5.6 Hz, 6-C*H*), 5.23 (1H, dd, *J*=5.6, 2.6 Hz, 5-C*H*), 6.26 (1H, s, N*H*), 7.28–7.81 (9H, m, Ar–H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 21.4, 28.7, 47.3, 57.6, 127.5, 128.0, 129.7, 129.9, 130.3, 130.6, 131.3, 143.5, 167.4, 192.3. Anal. Calcd for $C_{18}H_{17}NO_2S$: C, 69.43; H, 5.50; N, 4.50. Found: C, 69.38; H, 5.58; N, 4.44.

4.3. X-ray crystallographic determination of compound 3a

Data were collected at room temperature on an Enraf-Nonius MACH 3 four-circle diffractometer (Mo Kα radiation, λ=0.71073 Å). The data collection, integration and data reduction for **3a** were performed using CAD-4 EXPRESS and XCAD4 programs and an empirical absorption correction was applied using Ψ scan method. The unit cell parameters were determined by least square fitting of 25 randomly selected strong reflections and an empirical absorption correction was applied using the azimuthal scan method. The structure was solved by direct methods (SHELXS 97) and subsequent Fourier synthesis and refined by full matrix least

squares on SHELXL 97 for all non-hydrogen atoms for **3a**. All hydrogen atoms were placed in calculated positions.

Crystallographic data for compound **3a**: Triclinic, Space group $P-1$, $a=5.687$ Å, $b=10.691$ Å, $c=13.578$ Å, $V=742.6$ Å^3, $Z=2$, $F(000)=312$, $\mu=0.221$ mm^{-1}, $D_c=1.33$ mg/m^3. The reflections collected were 1575 of which 1557 unique [$R_{(int)}=0.0093$]; 1122 reflections $I>2\sigma(I)$, $R_1=0.0384$ and $\omega R_2=0.1007$ for 1122 [$I>2\sigma(I)$] and $R_1=0.0641$ and $\omega R_2=0.1169$ for all (1557) intensity data. Goodness of fit=1.000, residual electron density in the final Fourier map was 0.174 and -0.165 e Å^{-3}. The Cambridge Crystallographic Data Centre number associated to this compound is 738670.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2011.06.107. These data include MOL files and InChIKeys of the most important compounds described in this article.

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