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ScienceDirect
Tetrahedron 63 (2007) 11086–11092
Tetrahedron

Amino acid catalyzed thio-Michael addition reactions

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Received 30 April 2007; revised 24 July 2007; accepted 10 August 2007
Available online 15 August 2007

Abstract—Using amino acid as a catalyst, an inexpensive, nontoxic, environmentally friendly, metal-free reaction procedure for C–S bond formation via thio-Michael addition reaction has been developed. The thio-Michael addition products were obtained in excellent yields under mild and neutral conditions. This metal-free catalytic protocol was found to be a good alternative to the existing metal catalyst methodology for the thio-Michael addition reaction.

1. Introduction

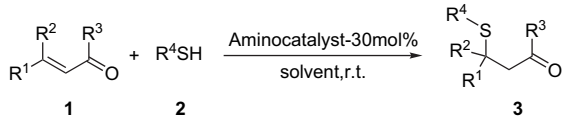
The thio-Michael addition reaction has emerged as one of the most powerful tools for C–S bond formation.[1] Thio-Michael addition provides a widespread synthetic utility in organic chemistry (i) for chemoselective protection of olefinic double bond in unsaturated carbonyl compound,[2] (ii) for the generation of acyl vinyl cation equivalents[3] and homoenolate anion equivalents,[4] and (iii) for the synthesis of medicinally important compounds like Diltiazem.[5] Generally, the 1,4-conjugate addition of a thiol requires activation of acceptor olefin by Lewis acid or deprotonation of thiol by base.[6] Consequently, there are several methods reported for thiol addition to electron deficient olefins such as $Bi(OTf)_3$,[7] $InBr_3$,[8] $Hf(OTf)_3$,[9] alumina in DMF,[10] NafionSAC-13,[11] iodine,[12] $InCl_3$,[13] and $Cu(BF_4)_2 \cdot xH_2O$.[14] More recently, ionic liquids have attracted much attention in thiol addition due to its green chemistry. Yadav et al. used $[Bmin]PF_6/H_2O$,[15] while Ranu et al. reported thiol addition in $[Pmin]PF_6$.[16] However, ionic liquids have been shown to have serious drawbacks, especially imidazolium systems with PF_6 and BF_4 anions, which are as toxic as benzene to certain aquatic ecosystems and also liberate hazardous HF during recycling. In addition, the high cost and disposability of these solvents also limit their utility. The various disadvantages of previously reported methods such as long reaction time, high reaction temperatures, use of expensive catalysts, stringent dry conditions, moderate yields, use of stoichiometric amount of catalysts, and expensive metal precursors that are harmful to the environment necessitates the development of newer methods for thio-Michael addition.[6–16]

Thus, the development of an environmentally benign and metal-free catalytic reaction is currently our objective. Recently, aminocatalysis has gained much importance in the field of asymmetric organic synthesis. Most attention has been focused on the use of proline, an inexpensive and readily available amino acid in either L or D form. L-Proline has been found to be very effective in enamine based direct catalytic asymmetric aldol,[17] Mannich,[18] Diels–Alder,[19] and Knoevenagel type of reactions.[20]

Herein, we disclose the (*S*)-proline and other amino acid catalyzed, green, cost effective, environment friendly, and high yielding procedure for the synthesis of thio-Michael adducts.

2. Results and discussion

The focus of our project was to develop a direct amino acid catalyzed thio-Michael reaction with a broad variety of enones (**1**) with alkyl and aryl thiols (**2**) to obtain the thio-Michael adduct (**3**) (Scheme 1).



1 2 3

Scheme 1. Amino acid catalyzed thio-Michael conjugate addition.

For the optimization process, we first examined the catalytic efficiency of (*S*)-proline in our model reaction of chalcone (**1a**) with thiophenol (**2a**) in methanol at room temperature. The conjugated addition product (**3a**) was obtained within 2–3 min in high yield. In addition to (*S*)-proline, we also

Keywords: Thio-Michael; Aminocatalysis; Amino acid; Green synthesis.
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0040–4020/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2007.08.033

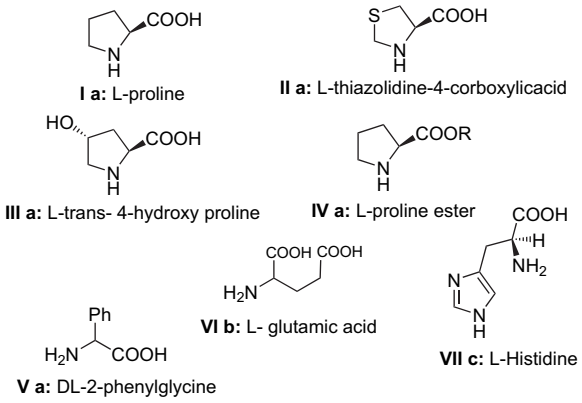


Figure 1. Aminocatalysts used in thio-Michael reaction.

investigated other amino acid catalysts (**IIa**–**VIIc**) and their ability to mediate the model reaction (Fig. 1).

In order to obtain better results in terms of yield and enantioselectivity, we applied these amino acid catalysts to our model reaction of chalcone **1a** with thiophenol **2a** under two different solvent systems; (i) methanol at −20 °C, as lowering in temperature induces better asymmetric induction, and (ii) methanol at room temperature (Table 1).

It was observed that the catalytic effects of cyclic neutral amino acids (**Ia**), (**IIa**) and (**IIIa**) were almost similar but when proline ester (**IVa**) was taken as the catalyst, the product yield decreased. Neutral amino acid DL-phenylglycine (**IVa**), acidic amino acid glutamic acid (**VIb**), and basic amino acid histidine (**VIIc**), which have a primary amino group, when used as catalysts were found to be less effective in comparison to a secondary amino group. The results of Table 1 led us to assume that cyclic amino acid with a secondary nitrogen is essential for better catalytic activity as it has provided the highest yield of product in the shortest time.

Replacing the CH_2 of proline (**Ia**) by S (**IIa**) and with CHOH (**IIIa**) gave comparable yields but required much longer time. Proline (**Ia**), thio-proline (**IIa**), and hydroxyl-proline (**IIIa**) (Table 1, entries 2–4) in methanol at −20 °C as well as in methanol at room temperature followed the same trend and provided synthetically useful yields with modest stereocontrol. Although thiazolidine-4-carboxylic acid gave good results, (*S*)-proline (**Ia**) was found to be the best catalyst from efficiency and commercial point of view and it was chosen for further optimization.

We also examined effect of solvents and catalyst loading on the (*S*)-proline catalyzed thio-Michael reaction of chalcone (**1a**) with thiophenol (**2a**) in order to enhance the selectivity.

Interestingly, we observed that the dielectric constants of the solvents and temperature had a remarkable effect on the (*S*)-proline catalyzed thio-Michael reaction (Table 2). The reaction in water did not proceed at all due to the immiscibility of the starting chalcones in water. Halogenated solvents $CHCl_3$ and DCM (Table 2, entries 6 and 7) gave better yield. We also carried out the reaction in toluene at −20 °C but very low yield was obtained. As all solvents gave moderate to good yield, further, we tried 10, 20, and 30 mol % of (*S*)-proline in methanol at room temperature (Table 2, entries 9–11). Surprisingly at 30 mol % of (*S*)-proline, the reaction took 3 min to complete and the product itself precipitated in the reaction mixture. The results clearly indicate that solvent of high dielectric constants facilitate the amino catalytic reaction (Table 2). Methanol (de=30) was found to be superior to acetonitrile (de=36.3) as it probably enhances the enamine formation through hydrogen bonding. Therefore, at 30 mol % of (*S*)-proline, methanol is the solvent of choice.

The thio-Michael reaction of compounds **3a**–**d**, **3f**, and **5a** with (*S*)-proline in methanol at −20 °C was performed and their enantioselectivity was determined by HPLC Chiralpak OD-H column (Table 3). The synthesized compounds had enantiomeric excess in the range of 24–45%. As the enantioselectivity of this process was low (45%), the yield, short reaction time, and exceptional simplicity of the procedure prompted us to investigate the scope of this novel amino catalytic reaction.

In order to study the catalytic potentiality of (*S*)-proline catalyzed thio-Michael reaction, we performed the conjugate addition of aryl as well as alkyl thiols to various substituted chalcones (Schemes 2 and 3). Excellent results were obtained in each case. The reaction was in general very fast

Table 1. Aminocatalysts screened for the direct thio-Michael reaction of chalcone (**1a**) and thiophenol (**2a**)[a–e]

Entry	Aminocatalyst[a]		Methnol at −20 °C		MeOH at rt		
			t[b]	Yield[c]	ee %[d]	t[b]	Yield[c]
1	None		—	—	—	—	—
2	**Ia**	Neutral	1.2	92	39	3[e]	98
3	**IIa**	Neutral	2.0	68	20	0.5	92
4	**IIIa**	Neutral	2.5	65	10	1.2	90
5	**IVa**	—	5.5	58	<10	2.0	65
6	**Va**	Neutral	5.0	45	<8	1.8	70
7	**VI b**	Acidic	5.6	35	<5	2.5	35
8	**VI1c**	Basic	8.0	25	nd	3.0	30

[a] Reaction conditions: 30 mol % of amino catalyst.
[b] Time in hour.
[c] Isolated yield (%).
[d] Determined by chiral HPLC (Chiralpak OD-H, *n*-hexane/*i*-PrOH 98:2, λ=270 nm).
[e] Time in minute.

Table 2. Optimization studies of (*S*)-proline catalyzed thio-Michael reaction between **1a** and **2a** under different organic solvents[a–d]

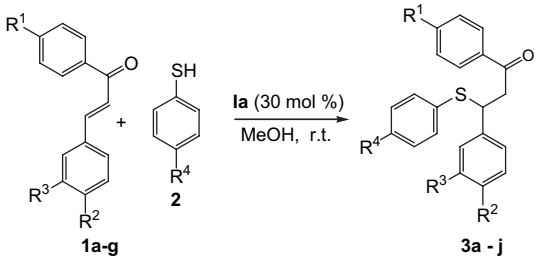
Entry	Solvent[a]	de[b]	Condition[c]	Yield (%)[d]
1	Neat	—	1 equiv, rt, 2–3 days	15
2	H_2O	—	1 equiv, rt, 24 h	—
3	C_6H_6	2.27	30 mol %, rt, 8 h	40
4	Toluene	2.37	30 mol %, rt, 6 h	65
5	Toluene	2.37	35 mol %, −20 °C, 6 h	35
6	$CHCl_3$	4.64	30 mol %, rt, 2 h	70
7	DCM	8.9	30 mol %, rt, 1.8 h	74
8	CH_3CN	36.2	30 mol %, rt, 2.0 h	80
9	MeOH	30	10 mol %, rt, 1.2 h	65
10	MeOH	30	20 mol %, rt, 0.5 h	88
11	MeOH	30	30 mol %, rt, 3 min	98

[a] Reaction conditions: distilled solvents used, no need to dry.
[b] Dielectric constants of solvents.
[c] mol % of (*S*)-proline.
[d] Isolated yields.

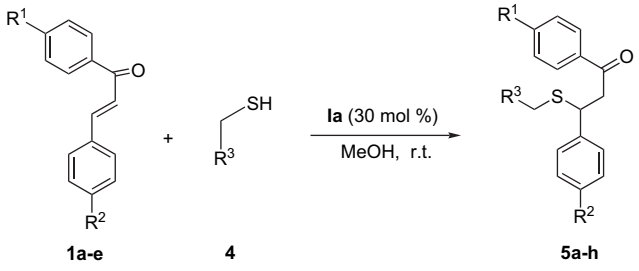
Table 3. Asymmetric thio-Michael addition catalyzed by (*S*)-proline[a–e]

Entry	Product	ee %[b]	Yield [c]	t[d]	t_R minor[e]	t_R major[e]
1	**3a**	45	92	1.2	11.3	12.1
2	**3b**	25	94	1.2	11.5	12.9
3	**3c**	24	90	1.5	19.1	20.0
4	**3d**	25	92	1.3	21.6	23.1
5	**3f**	39	94	0.5	14.7	17.0
6	**5a**	2	88	2.8	4.51	5.21

[a] Reaction conditions: chalcone (1 mmol), thiol (1.5 mmol thiophenol, and 2.0 mmol of ethanthiol), 30 mol % of (*S*)-proline stir at −20 °C in methanol.
[b] Determined by chiral HPLC (Chiralpak OD-H, *n*-hexane/*i*-PrOH 98:2, λ=270 nm).
[c] Isolated yield (%) of pure products after crystallization.
[d] Time in hour.
[e] Retention time of minor and major isomer.



Scheme 2.



Scheme 3.

and completed within 5–10 min. It was gratifying to observe the conjugate addition product also precipitates from the reaction mixture in most of these cases. Electronic factors play a crucial role in this reaction. It was observed that the chalcone containing electron donating group facilitates the rate and yield of reaction while the chalcone carrying the electron withdrawing substituent (Table 4, entries 8–10) comparatively decreases the rate and yield of reaction. Similarly electronic factors in thiols also influence the rate of reaction. Generally rapid conversion and excellent yield was observed when the reaction was carried out with aryl thiols (Scheme 2).

While, the (*S*)-proline catalyzed conjugate addition of alkyl thiols and mercapto carboxylic acid to chalcones required longer reaction time in comparison to aryl thiols (Scheme 3). The results of Schemes 2 and 3 are summarized in Table 4.

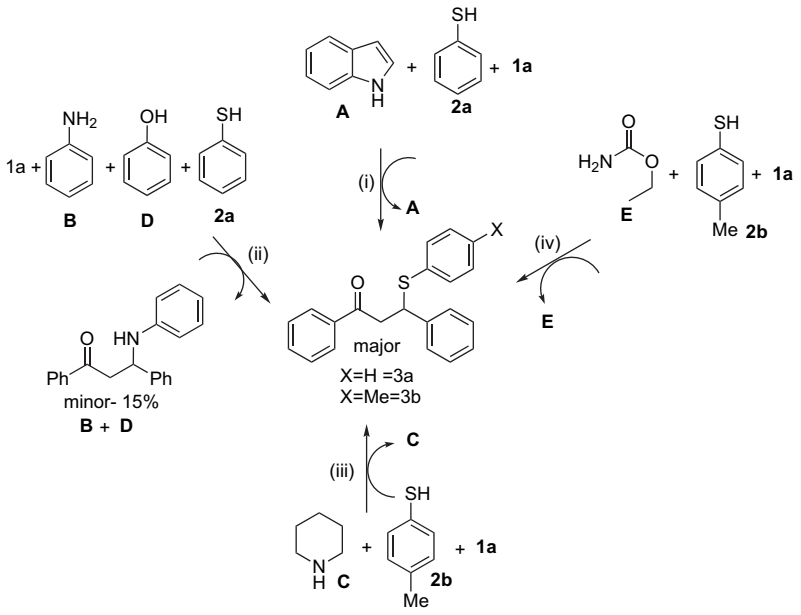
On comparing our results with the recently reported methods, we found that (*S*)-proline efficiently catalyzed the reaction of chalcone with thiol in methanol in shortest time. As recently reported copper(II) tetrafluroborate required longer reaction time for conjugate addition of thiol to chalcone in methanol at room temperature and not compatible with weakly polar solvents (DCM, THF, dioxane, etc.).[14] Molten tetra butyl bromide fails to react with chalcone.[21] $Zn(ClO_4)_2 \cdot 6H_2O$ also require refluxing condition and longer reaction time for thiol additon.[22] $InCl_3$ (10 mol %) catalyzed thiol addition to chalcone strictly required dry condition as this reaction was very much moisture sensitive and did not catalyze reaction in other conventional solvents.[13]

Another notable feature of the amino catalytic reaction lies in its chemoselectivity. To explore the intermolecular chemoselectivity of this procedure, we carried out a competitive study of 1,4-conjugate addition of other nucleophiles such as amines, carbamates, and phenols to 1,3-diphenylpropenone (**1a**) in the presence of different thiols. It was observed that all the reactions proceeded with high chemoselectivity in favor of C–S bond formation and leading to high yields of the thio-Michael adduct (Scheme 4).

Table 4. (*S*)-Proline catalyzed thio-Michael addition of aryl as well as alkyl thiols to diarylpropenones (Schemes 2 and 3)[a–h]

Entry	R^1	R^2	R^3	R^4	t[d]	Yield[e]	Product[f,h]	Entry	R^1	R^2	R^3	t[d]	Yield[e]	Product[g,h]
1	H	H	H	H	2	98	**3a**	11	H	H	Me	30	90	**5a**
2	H	H	H	CH_3	2	96	**3b**	12	H	H	CO_2H	60	82	**5b**
3	OCH_3	H	H	H	3	98	**3c**	13	H	H	CH_2CO_2H	60	88	**5c**
4	OCH_3	H	H	CH_3	7	92	**3d**	14	OCH_3	H	Me	35	89	**5d**
5	H	OCH_3	H	H	3	94	**3e**	15	OCH_3	H	CH_2CO_2H	60	78	**5e**
6	OCH_3	OCH_3	H	H	5	97	**3f**	16	OCH_3	OCH_3	Me	30	90	**5f**
7	OCH_3	OCH_3	H	CH_3	5	98	**3g**	17	OH	H	Me	40	70	**5g**
8	CH_3	H	Cl	H	10	80	**3h**	18	H	C_4H_4O	Me	30	80	**5h**
9	CH_3	H	Cl	CH_3	8	82	**3i**	—	—	—	—	—	—	—
10	OH	H	H	H	15	89	**3j**	—	—	—	—	—	—	—

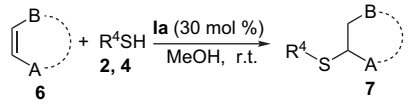
[a] Reaction conditions: 1 equiv of enone, 1.8 equiv of aryl thiol, 2.0 equiv of alkyl thiol, and 2.5 equiv of mercapto corboxylic acid, 30 mol % of L-proline.
[b] MeOH as a solvent (2–3 mL).
[c] All reactions were carried out at room temperature.
[d] Time in minute.
[e] Isolated yield (%).
[f] Scheme 2.
[g] Scheme 3.
[h] All products were characterized by ^{1}H NMR, ^{13}C NMR, IR spectroscopy, and MS.



Scheme 4. (*S*)-Proline catalyzed intermolecular chemoselective conjugate addition of thiol to chalcone. Reaction conditions: (i) **1a** (1 mmol), **A** (2 mmol), **2a** (1.5 mmol), 30 mol % (*S*)-proline, methanol, rt (1–12 h); (ii) **1a** (1 mmol), **B** (2 mmol), **D** (2 mmol), **2a** (1.5 mmol), 30 mol % (*S*)-proline, methanol, rt (2–3 h); (iii) **1a** (1 mmol), **C** (2 mmol), **2b** (1.5 mmol), 30 mol % (*S*)-proline, DMSO, rt; (iv) **1a** (1 mmol), **E** (2 mmol), **2b** (1.5 mmol), 30 mol % (*S*)-proline, methanol, rt.

To further expand the scope of the (*S*)-proline catalyzed C–S bond forming reaction, we next applied our optimized procedure to acyclic and cyclic enones. The (*S*)-proline catalyzed thio-Michael addition was found equally compatible with acyclic and cyclic enones. The results are summarized in Table 5.

Table 5. (*S*)-proline catalyzed thio-Michael addition of aryl as well as alkyl thiols to acyclic and cyclic enones[a–d]



Entry	A	B	R^4	*t* (min)	Yield[d]
19	H	COMe	Ph	3	98
20	H	COMe	4-Me-Ph	2	96
21	H	COMe	Et	5	90
22	H	CN	Ph	3	94
23		$4,4\text{-}(Me)_2C_6H_6O$	Ph	10	92
24		$4,4\text{-}(Me)_2C_6H_6O$	4-Me-Ph	8	89
25		C_6H_8O	Ph	5	94

[a] Reaction conditions: 1 equiv of acyclic enone, 1.5 equiv of aryl thiol, 2.0 equiv of alky thiol, and 30 mol % of (*S*)-proline.
[b] MeOH as a solvent (2–3 mL).
[c] All reactions were carried out at room temperature.
[d] Isolated yield (%).

3. Conclusion

In conclusion, we have developed a simple and efficient amino acid catalyzed methodology for the synthesis of thio-Michael adducts. The methodology was found to be high yielding, green, and cost effective. Short reaction time, room temperature, high yield, and avoidance of anhydrous conditions should make this protocol a useful alternative to existing methods for the synthesis of thio-Michael adducts.

4. Experimental

4.1. Materials and general

All the reactions were carried out at room temperature, that is, 28–32 °C. Unless otherwise specified, all the reagents were purchased from Sigma–Aldrich Chemical Co and Lancaster, and were used directly without any further purification. NMR spectra were obtained using the Brucker DRX 200 MHz spectrometer. Chemical shifts (δ) are given in parts per million relative to TMS and coupling constants (*J*) in hertz. Mass spectra were obtained using JEOL SX-102 (FAB^+) instrument. Elemental analysis was preformed using a Perkin–Elmer Autosystem XL Analyzer. Reactions were monitored by thin layer chromatography (TLC) carried out on 0.25 mm silica gel plates visualized with UV light.

4.2. General procedure for amino catalytic thio-Michael addition

4.2.1. Typical experimental procedure for conjugate addition of aryl thiols to chalcone (Scheme 2).

4.2.1.1. Representative procedure for the synthesis of compounds of Scheme 2 [1,3-Diphenyl-3-phenylsulfanyl-propan-1-one]. To a magnetically stirred mixture of 1,3-diphenylpropenone (**1a**) (1 mmol) and (*S*)-proline (**Ia**) (30 mol %) in methanol (1–2 mL), thiophenol (1.8 mmol) was added dropwise with the help of syringe. The reaction mixture was stirred at room temperature. The precipitation occurs within 2–3 min. The precipitate was filtered, washed with methanol, and crystallized by ethyl acetate and hexane to obtain pure product in high yield. The

same procedure was followed for the synthesis of all compounds of Scheme 2.

4.2.2. Typical experimental procedure for conjugate addition of alkyl thiols to chalcone (Scheme 3).

4.2.2.1. Representative procedure for the synthesis of compounds of Scheme 3 [3-Ethylsulfanyl-1,3-diphenyl-propan-1-one]. In a typical experiment 1,3-diphenylpropenone (**1a**) (1 mmol) and (*S*)-proline (**Ia**) (30 mol %) in MeOH (2–3 mL) were mixed together and then ethanthiol (**2a**) (2 mmol) was added dropwise with help of syringe. The solution was stirred at room temperature under an air atmosphere for appropriate time of period. After the completion of the reaction (monitored by TLC and IR), the reaction mixture was worked up by simple extraction with ethyl acetate and water. The filtrate was evaporated under vacuum on a rotary evaporator to afford the desired product in high purity. The further purification was performed by crystallization with ethyl acetate and hexane. The above-described procedure was also used for the synthesis of compounds of Table 5.

4.2.3. Typical experimental procedure for the intermolecular chemoselective reaction (Scheme 4).

To a magnetically stirred mixture of 1,3-diphenylpropenone (**1a**) (1 mmol), and (*S*)-proline (**Ia**) (30 mol %) in MeOH (2 mL) indole (2 mmol) and thiophenol (1.5 mmol) were added at room temperature. The reaction was stirred for appropriate time. The precipitate was filtered and washed with water and methanol. The solid residue was crystallized by ethyl acetate and hexane to afford the pure product in high yield. The product was characterized by ^{1}H and ^{13}C NMR spectroscopy, it gave the thio-Michael adduct as a sole product. The same protocol was also applied for other nucleophiles.

All the compounds reported in Tables 4 and 5 were properly characterized by their spectroscopic data. The IR, ^{1}H and ^{13}C NMR spectral data, and elemental analysis, confirms the identities of compounds. The compounds (**1**, **2**, **19**–**22**, **25**)[8–16,21,22] that are known their spectroscopic data was found to be consistent with that of reported in literature. The spectroscopic details of all compounds are given below.

4.3. Spectroscopic and analytical data of compounds

4.3.1. 1,3-Diphenyl-3-phenylsulfanyl-propan-1-one (1). White solid; mp 118–120 °C [Found: C, 79.33; H, 5.74. $C_{21}H_{18}OS$ requires C, 79.21; H, 5.70%.]; ν_{max} (KBr) 3042, 1679, 1592 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.85 (2H, d, *J* 7.5 Hz, Ph), 7.54–7.13 (13H, m, Ph), 4.91 (1H, dd, *J* 7.6, 6.0 Hz, SC*H*), 3.73–3.50 (2H, m, COCH_2); δ_C NMR (50 MHz, $CDCl_3$) 197.4, 141.6, 137.1, 134.6, 133.6, 133.1, 129.2, 129.0, 128.8, 128.4, 128.2, 127.9, 127.7, 48.6, 45.1; *m*/*z* 318 (100, MH^+), 209 (80), 105 (65%).

4.3.2. 1-(4-Methoxy-phenyl)-3-phenyl-3-phenylsulfanyl-propan-1-one (3). White solid; mp 80–82 °C [Found: C, 75.80; H, 5.77. $C_{22}H_{20}O_2S$ requires C, 75.83; H, 5.79%.]; ν_{max} (KBr) 3429, 1665, 1602 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.83 (2H, d, *J* 8.8 Hz, Ph), 7.34–7.16 (10H, m, Ph), 6.86 (2H, d, *J* 8.8 Hz, Ph), 4.91 (1H, t, *J* 6.3 Hz, SC*H*), 3.83 (3H, s, O*Me*), 3.59–3.52 (2H, dd, *J* 6.2, 4.7 Hz, COCH_2); δ_C (50 MHz, $CDCl_3$) 195.8, 164.0, 141.7, 134.7, 133.0, 130.7, 130.3, 129.2, 128.8, 128.2, 127.8, 127.7, 114.1, 55.8, 48.7, 44.7; *m*/*z* 349 (80, MH^+), 297 (75), 239 (75), 135 (100%).

4.3.3. 1-(4-Methoxy-phenyl)-3-*p*-tolylsulfanyl-propan-1-one (4). White solid; mp 98–100 °C [Found: C, 75.80; H, 5.77. $C_{22}H_{20}O_2S$ requires C, 75.83; H, 5.79%.]; ν_{max} (KBr) 3420, 1683, 1600 cm^{-1}; δ_H (200 MHz $CDCl_3$) 7.83 (2H, d, *J* 8.8 Hz, Ph), 7.40–7.00 (9H, m, Ph), 6.86 (2H, d, *J* 8.8 Hz, Ph), 4.83 (1H, dd, *J* 6.4, 6.3 Hz, SC*H*), 3.85 (3H, s, O*Me*), 3.57–3.51 (2H, m, COCH_2), 2.29 (3H, s, *Me*); δ_C (50 MHz, $CDCl_3$) 196.0, 163.9, 141.8, 138.1, 133.8, 130.7, 130.0, 128.9, 128.7, 128.2, 127.6, 114.1, 55.8, 49.1, 44.5, 21.5; *m*/*z* 363 (85, MH^+), 239 (50), 135 (92%).

4.3.4. 3-(4-Methoxy-phenyl)-1-phenyl-3-phenylsulfanyl propan-1-one (5). White solid; mp 87–88 °C [Found: C, 75.80; H, 5.77. $C_{22}H_{20}O_2S$ requires C, 75.83; H, 5.79%.]; ν_{max} (KBr) 3445, 1683, 1580 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.85 (2H, d, *J* 7.4 Hz, Ph), 7.54–7.26 (10H, m, Ph), 6.78 (2H, d, *J* 8.6 Hz, Ph), 4.91 (1H, dd *J* 8.2, 6.0 Hz, SC*H*), 3.78 (3H, s, O*Me*), 3.59–3.52 (2H, m, COCH_2); δ_C (50 MHz, $CDCl_3$) 195.8, 164.0, 141.7, 134.7, 133.0, 130.7, 130.3, 129.2, 128.8, 128.2, 127.8, 127.7, 114.1, 55.8, 48.7, 44.7; *m*/*z* 349 (80, MH^+), 297 (75), 239 (75), 135 (100%).

4.3.5. 1,3-Bis-(4-methoxy-phenyl)-3-phenylsulfanyl-propan-1-one (6). White solid; mp 120–122 °C [Found: C, 72.96; H, 5.87. $C_{23}H_{22}O_3S$ requires C, 72.99; H, 5.86%.]; ν_{max} (KBr) 3435, 1670, 1599 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.83 (2H, d, *J* 8.8 Hz, Ph), 7.20–7.35 (7H, m, Ph), 6.86 (2H, d, *J* 8.8 Hz, Ph), 6.75 (2H, d, *J* 8.6 Hz, Ph), 4.89 (1H, t, *J* 6.1 Hz, SC*H*), 3.84 (3H, s, O*Me*), 3.74 (3H, s, O*Me*), 3.57–3.49 (2H, m, COCH_2); δ_C (50 MHz, $CDCl_3$) 196.1, 163.9, 159.0, 134.9, 133.6, 132.9, 130.8, 130.2, 129.2, 127.7, 114.1, 55.8, 55.6, 44.7, 48.1; *m*/*z* 378 (60, MH^+), 269 (100), 161 (30), 135 (42%).

4.3.6. 1,3-Bis-(4-methoxy-phenyl)-3-*p*-tolylsulfanyl-propan-1-one (7). White solid; mp 130–135 °C [Found: C, 73.46; H, 6.46. $C_{24}H_{24}O_3S$ requires C, 73.44; H, 6.16%.] ν_{max} (KBr) 3445, 1677, 1590 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.87 (2H, d, *J* 8.8 Hz, Ph), 7.25–7.20 (4H, m, Ph), 7.05 (2H, d, *J* 8.0 Hz, Ph), 6.90 (2H, d, *J* 8.8 Hz, Ph), 6.79 (2H, d, *J* 8.6 Hz, Ph), 4.88 (1H, t, *J* 6.1 Hz, SC*H*), 3.84 (3H, s, O*Me*), 3.74 (3H, s, O*Me*), 3.55–3.47 (2H, m, COCH_2), 2.29 (3H, s, *Me*); δ_C (50 MHz, $CDCl_3$) 196.2, 163.9, 159.0, 138.0, 133.7, 131.0, 130.7, 130.3, 130.0, 129.2, 114.1, 55.8, 55.6, 48.6, 44.7, 21.5; *m*/*z* 392 (50, MH^+), 269 (100%).

4.3.7. 3-(3-Chloro-phenyl)-3-phenylsulfanyl-1-*p*-tolyl-propan-1-one (8). White solid; mp 106–108 °C [Found: C, 72.08; H, 5.25. $C_{22}H_{19}ClOS$ requires C, 72.02; H, 5.22 %.] ν_{max} (KBr) 3420, 1674, 1601 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.80 (2H, d, *J* 7.7 Hz, Ph), 7.31–7.16 (11H, m, Ph), 4.89 (1H, t, *J* 7.0 Hz, SC*H*), 3.54 (2H, d, *J* 7.0 Hz, COCH_2), 2.39 (3H, s, *Me*); δ_C (50 MHz, $CDCl_3$) 196.1, 144.0, 143.8, 141.1, 133.7, 130.7, 129.2, 129.0, 128.7, 128.2, 128.0, 127.6, 126.6, 126.4, 47.3, 44.5, 22.8; *m*/*z* 367 (80, MH^+), 256 (100%).

4.3.8. 3-(3-Chloro-phenyl)-1-*p*-tolyl-3-*p*-tolylsulfanyl-propan-1-one (9). White solid; mp 100–104 °C [Found: C, 72.50; H, 5.60. $C_{23}H_{21}ClOS$ requires C, 72.52; H, 5.56%.] ν_{max} (KBr) 3420, 1674, 1601 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.77 (2H, d, *J* 7.8 Hz, Ph), 7.31–7.11 (10H, m, Ph), 4.83 (1H, t, *J* 7.2 Hz, SC*H*), 3.57 (2H, d, *J* 7.2 Hz, COCH_2), 2.40 (3H, s, *Me*), 2.32 (3H, s, *Me*); δ_C (50 MHz, $CDCl_3$) 196.6, 144.6, 144.0, 141.1, 133.9, 130.7, 129.9, 129.7, 128.5, 128.3, 128.2, 127.8, 126.8, 126.4, 47.6, 44.7, 22.0, 21.0; *m/z* 381 (70, MH^+), 256 (90%).

4.3.9. 1-(4-Hydroxy-phenyl)-3-phenyl-3-phenylsulfanyl-propan-1-one (10). White solid; mp 103–105 °C [Found: C, 75.46; H, 5.46. $C_{21}H_{18}O_2S$ requires C, 75.42; H, 5.43%.] ν_{max} (KBr) 3420, 1663, 1602 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.78 (2H, d, *J* 8.4 Hz, Ph), 7.42–7.16 (10H, m, Ph), 6.80 (2H, d, *J* 8.7 Hz, Ph), 4.89 (1H, t, *J* 7.1 Hz, SC*H*), 3.67–3.44 (2H, m, COCH_2); δ_C (50 MHz, $CDCl_3$) 196.6, 161.1, 141.5, 134.6, 133.1, 131.5, 131.2, 129.2, 128.8, 128.1, 127.9, 127.7, 115.8, 48.8, 44.6; *m/z* 334 (80, MH^+), 225 (92%).

4.3.10. 3-Ethylsulfanyl-1,3-diphenylpropan-1-one (11). White solid; mp 60–61 °C [Found: C, 75.53; H, 6.70. $C_{17}H_{18}OS$ requires C, 75.51; H, 6.71%.] ν_{max} (KBr) 3420, 1677, 1600 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.89 (2H, d, *J* 7.5 Hz, Ph), 7.54–7.39 (5H, m, Ph), 7.33–7.16 (3H, m, Ph), 4.55 (1H, t, *J* 7.0 Hz, SC*H*), 3.51 (2H, d, *J* 7.0 Hz, COCH_2), 2.41–2.29 (2H, m, CH_2Me), 1.13 (3H, t, *J* 7.3 Hz, CH_2*Me*); δ_C (50 MHz, $CDCl_3$) 197.3, 142.6, 137.2, 133.6, 129.0, 128.9, 128.5, 128.2, 127.6, 45.7, 44.4, 25.8, 14.7; *m/z* 269 (25, MH^+), 268 (100), 209 (40), 148 (10%).

4.3.11. 3-(3-Oxo-1,3-diphenyl-propylsulfanyl)-acetic acid (12). Yellow oil [Found: C, 67.96; H, 5.37. $C_{17}H_{16}O_3S$ requires 67.98; H, 5.35%.]; ν_{max} (KBr) 3407, 1620, 1598 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.82 (2H, d, *J* 7.4 Hz, Ph), 7.15–7.36 (8H, m, Ph), 4.52 (1H, t, *J* 6.9 Hz, SC*H*), 3.53–3.49 (4H, m, CH_2CH_2); δ_C (50 MHz, $CDCl_3$) 197.0, 175.1, 170.5, 141.0, 137.0, 133.7, 129.0, 128.5, 128.2, 127.9, 52.8, 41.4, 44.9; *m/z* 301 (60, MH^+), 209 (78).

4.3.12. 3-(3-Oxo-1,3-diphenyl-propylsulfanyl)-propionic acid (13). Yellow oil [Found: C, 68.78; H, 5.75. $C_{18}H_{18}O_3S$ requires C, 68.76; H, 5.77%.]; ν_{max} (KBr) 3407, 1600, 1598 cm^{-1} δ_H (200 MHz, $CDCl_3$) 7.88 (2H, d, *J* 7.1 Hz, Ph), 7.59–7.19 (8H, m, Ph), 4.59 (1H, t, *J* 6.9 Hz, SC*H*), 3.52 (2H, d, *J* 6.9 Hz, COCH_2), 2.60–2.52 (4H, m, SCH_2CH_2CO_2H); δ_C (50 MHz, $CDCl_3$) 197.1, 177.3, 142.0, 137.0, 133.7, 129.0, 128.5, 128.2, 127.9, 45.6, 44.9, 34.4, 26.4; *m/z* 315 (20, MH^+), 301 (80), 209 (88), 105 (100%).

4.3.13. 3-Ethylsulfanyl-1-(4-methoxy-phenyl)-3-phenyl-propan-1-one (14). White solid; mp 90–92 °C [Found: C, 71.98; H, 6.77. $C_{18}H_{20}O_2S$ requires C, 71.96; H, 6.71%.]; ν_{max} (KBr) 3428, 1680, 1600 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.87 (2H, d, *J* 8.8 Hz, Ph), 7.32–7.19 (5H, m, Ph), 6.86 (2H, d, *J* 8.8 Hz, Ph), 4.54 (1H, t, *J* 7.0 Hz, SC*H*), 3.82 (3H, s, O*Me*), 3.45 (2H, d, *J* 7.0 Hz, COCH_2), 2.40–2.28 (2H, m, CH_2Me), 1.15 (3H, t, *J* 7.3 Hz, *Me*); δ_C (50 MHz, $CDCl_3$) 195.0, 164.0, 141.7, 134.7, 133.0, 130.7, 130.3, 129.2, 128.8, 128.2, 127.8, 127.7, 114.1, 55.8, 45.3, 44.6, 25.8, 14.7; *m/z* 301 (80 MH^+), 289 (45), 239 (80), 116 (92%).

4.3.14. 3-[3-(4-Methoxy-phenyl)-3-oxo-1-phenyl-propylsulfanyl]-propionic acid (15). Yellow semi solid [Found: C, 66.30; H, 5.80. $C_{19}H_{20}O_4S$ requires C, 71.96; H, 6.71%.]; ν_{max} (KBr) 3407, 1602, 1599, 1502 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.91 (2H, d, *J* 8.8 Hz, Ph), 7.43–7.26 (5H, m, Ph), 6.92 (2H, d, *J* 8.8 Hz, Ph), 4.58 (1H, t, *J* 6.9 Hz, SC*H*), 3.85 (3H, s, O*Me*), 3.49 (2H, d, *J* 6.9 Hz, COCH_2), 2.60–2.51(4H, m, SCH_2CH_2CO_2H); δ_C (50 MHz, $CDCl_3$) 195.7, 178.0, 142.2, 132.7, 130.8, 130.1, 129.0, 128.2, 127.8, 114.1, 55.8, 45.2, 34.7, 26.4; *m/z* 345 (80, MH^+), 314 (20%).

4.3.15. 3-Ethylsulfanyl-1,3-Bis-(4-methoxy-phenyl)-propan-1-one (16). White solid; mp 140–141 °C [Found: C, 69.10; H, 6.72. $C_{19}H_{22}O_3S$ requires C, 69.06; H, 6.71%.]; ν_{max} (KBr) 3430, 1680, 1669 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.87 (2H, d, *J* 8.8 Hz, Ph), 7.30 (2H, d, *J* 8.6 Hz, Ph), 6.88–6.80 (4H, m, Ph), 4.51 (1H, t, *J* 7.0 Hz, SC*H*), 3.85 (3H, s, O*Me*), 3.77 (3H, s, O*Me*), 3.43 (2H, d, *J* 7.1 Hz, COCH_2), 2.38–2.28 (2H, m, CH_2Me), 1.12 (3H, t, *J* 7.3 Hz, *Me*); δ_C (50 MHz, $CDCl_3$) 196.0, 163.9, 158.9, 134.6, 130.8, 130.3, 129.2, 114.2, 55.8, 55.6, 45.5, 44.0, 25.7, 14.7; *m/z* 330 (20, MH^+), 269 (80%).

4.3.16. 3-Ethylsulfanyl-1-(4-hydroxy-phenyl)-3-phenyl-propan-1-one (17). White semi solid [Found: C, 71.4; H, 6.38. $C_{17}H_{18}O_2S$ requires C, 71.30; H, 6.34%.]; ν_{max} (KBr) 3422, 1673, 1605 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.85 (2H, d, *J* 9.8 Hz, Ph), 7.81–7.15 (5H, m, Ph), 6.84 (2H, d, *J* 7.7 Hz, Ph), 4.51 (1H, t, *J* 7.1 Hz, SC*H*), 3.46 (2H, d, *J* 7.1 Hz, COCH_2), 2.41–2.20 (2H, m, CH_2Me), 1.10 (3H, t, *J* 7.3 Hz, *Me*); δ_C (50 MHz, $CDCl_3$) 197.3, 161.7, 142.4, 131.6, 131.3, 129.7, 128.9, 128.1, 127.6, 116.0, 45.3, 44.8, 25.8, 14.7; *m/z* 286 (50, MH^+), 224 (75%).

4.3.17. 3-Furan-2-yl-1-(4-methoxy-phenyl)-3-phenyl-3-phenylsulfanyl-propan-1-one (18). White semi solid [Found: C, 70.9; H, 5.38. $C_{20}H_{18}O_3S$ requires C, 70.9; H, 5.36%.]; ν_{max} (KBr) 3422, 1683 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.80 (2H, d, *J* 8.8 Hz, Ph), 7.35 (1H, m, Ph), 7.22–7.11 (5H, m, Ph), 6.80 (2H, d, *J* 8.8 Hz, Ph), 6.09–6.07 (1H, m, Ph), 5.90 (1H, d, *J* 3.1 Hz, Ph), 4.92 (1H, t, *J* 6.9 Hz, SC*H*), 23.69 (3H, s, O*Me*), 3.50–3.30 (2H, m, COCH_2); δ_C (50 MHz, $CDCl_3$) 195.4, 164.1, 153.9, 142.3, 131.6, 131.3, 129.7, 128.9, 128.1, 127.6, 114.2, 110.7, 109.2, 107.7, 55.9, 42.2, 42.0; *m/z* 339 (20, MH^+), 228 (75), 135 (60%).

4.3.18. 4,4-Dimethyl-3-phenylsulfanyl-cyclohexanone (23). White crystalline solid; mp 66–68 °C [Found: C, 71.78; H, 7.76. $C_{14}H_{18}OS$ requires C, 71.75; H, 7.74%.]; ν_{max} (KBr) 3435, 1710 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.43–7.38 (2H, m, Ph), 7.34–7.24 (3H, m, Ph), 3.21–3.13 (1H, m, S*CH*), 2.62–2.55 (2H, m, CH_2), 2.48–2.34 (2H, m, CH_2), 1.89–1.87 (1H, m, CH_2), 1.86–1.61 (1H, m, CH_2), 1.28 (3H, s, *Me*), 1.22 (3H, s, *Me*); δ_C (50 MHz, $CDCl_3$) 209.4, 135.0, 133.1, 129.5, 127.8, 58.0, 45.8, 39.0, 38.2, 35.0, 29.4, 21.4; *m/z* 234.

4.3.19. 4,4-Dimethyl-3-*p*-tolylsulfanyl-cyclohexanone (24). Yellow solid; mp 75–78 °C; ν_{max} (KBr) 3432, 1709 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.39–7.25 (4H, m, Ph), 3.13–3.05 (1H, m, S*CH*), 2.59–2.52 (2H, m, CH_2), 2.40–2.37 (2H, m, CH_2), 2.31(3H, s, *Me*), 1.87–1.84 (1H, m, CH_2), 1.80–1.57 (1H, m, CH_2), 1.27 (3H, s, *Me*), 1.20 (3H, s, *Me*); δ_C (50 MHz, $CDCl_3$) 209.6, 134.3, 133.8, 131.2, 130.2, 58.5, 45.7, 39.0, 38.3, 35.0, 29.4, 21.4; *m*/*z* 248.

Acknowledgements

We are thankful to CSIR for the financial assistance. We are thankful to Mr. R. K. Purshottam for HPLC analysis.

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