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The first regio- and diastereoselective direct introduction of α-mercaptoacetic acid/amide units into Morita–Baylis–Hillman acetates

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ABSTRACT

The exposure of Morita–Baylis–Hillman acetates to mercaptoacetyl transfer agent, 2-methyl-2-phenyl-1,3-oxathiolan-5-one, in the presence of 1,4-diazabicyclo[2.2.2]octane enables the regio- and stereoselective allylic substitution through a tandem S_N2'–S_N2' mechanism. The product thus formed in situ undergoes selective hydrolysis with water in the presence of $CeCl_3$/NaI·$7H_2O$, and aminolysis of the 1,3-oxathiolan-5-one ring to afford functionally rich α-mercapto acids and α-mercapto amides, respectively. Operational simplicity, ambient temperature, excellent yield (81–96%), high diastereoselectivity (>94%), and recovery and recycling of the by-product formed are the salient features of the present synthetic protocol.

Morita–Baylis–Hillman (MBH) adducts bearing allylic hydroxyl and Michael acceptor units and their derivatives have been illustrated as valuable synthons and starting materials for the generation of diverse molecular skeletons employing simple alternatives.[1] Especially, regioselective introduction of nucleophiles at either α- or γ-position of the MBH acetates enables the construction of a variety of bioactive molecules and has become a powerful tool in synthetic organic chemistry.[2]

Synthesis of amides is important in many areas of chemistry, including peptide, polymer, and complex molecule synthesis.[3] Furthermore, mercaptoacetic acid derivatives have been found to be oxytocin inhibitors in the avian vasodepressor (AVD) assay.[4a] As regards the chemical point of view, α-mercapto acids have been utilized as substrates for the synthesis of bioactive molecules and medicines, and are also used as reagents for the identification of carbonyl compounds.[5] The medicinal and synthetic utility of α-mercapto acids and their amides is the major driving force for attracting organic and medicinal chemists to devise their synthesis.[4]

In this Letter, we report a conceptually new and practical use of MBH adducts in regio-/diastereoselective formation of α-mercapto acids/amides (Fig. 1) with several diversity points, which could be tailored further in a multitude of synthetic organic transformations. This has been achieved by an easy and direct installation of versatile functional groups such as mercapto, carboxylic acid, and amide on MBH adducts, which already contain three chemospecific

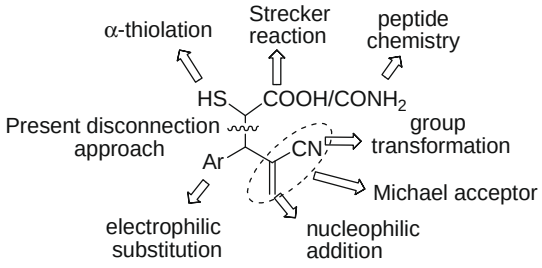

Figure 1. Designed and synthesized diversity-rich MBH acetate-derived α-mercapto acids and their amides.

functionalities, that is, hydroxy, alkene, and electron-withdrawing groups. The present one-pot functionalization of MBH adducts is an outcome of our continuous interest in new methodology development,[6] especially using MBH adducts as starting materials.[7]

Initially, we tried mercaptoacetic acid in the present synthetic protocol for mercaptoacetylative S_N2 reaction of MBH acetates **2**, but were not successful, probably due to the presence of free –COOH and –SH groups. Instead, we turned our attention to block the –COOH and –SH groups of mercaptoacetic acid and thus activate its methylene group by converting it into 2-methyl-2-phenyl-1,3-oxathiolan-5-one **1** (Scheme 1),[8] which not only acted as mercaptoacetyl transfer agent for the synthesis of α-mercapto acids but also provided a completely new route to α-mercapto amides. Recently, Moorthy and Singhal have described a highly selective conversion of nitriles to amides.[9] For increasing the diver-

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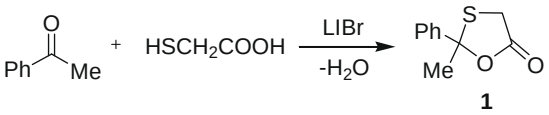


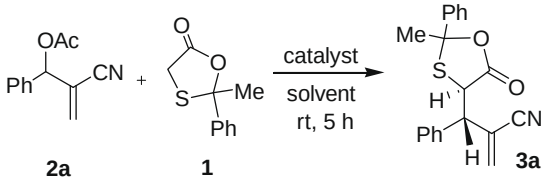
Scheme 1. Formation of the mercaptoacetyl transfer agent, 2-methyl-2-phenyl-1,3-oxathiolan-5-one **1**.

sity points in MBH adducts **2**, we attempted to introduce an additional amide unit incorporating –SH functionality at their α-position while keeping the nitrile group of **2** intact. For this purpose we utilized the masked mercaptoacetic acid **1**, which worked well in the envisaged synthetic protocol and is the cornerstone in our approach presenting its novel utilization in MBH chemistry.

In most of the cases, a nucleophilic attack on MBH acetates **2** takes place either at γ-carbon via S_N2' reaction,[1,2,10] or directly at α-position by means of base-promoted tandem S_N2'–S_N2'reaction[1i,2a,11,12] and through a Pd-catalyzed coupling reaction.[13] Recently, Chen et al. have reported a direct substitution at α-position of MBH acetates using Lewis acid catalysts,[14] which triggered us to investigate the scope of Lewis acids in the present direct nucleophilic substitution at α-position with the active methylene compound **1**.

Thus, we investigated the optimization of the reaction conditions in regard to both catalyst and solvent. Here, MBH acetate **2a** and 2-methyl-2-phenyl-1,3-oxathiolan-5-one **1** were chosen as the model substrates for the present S_N2 reaction, and the reaction was performed at rt (Table 1). Amongst $FeCl_3$, $Cu(OTf)_2$, and Ag(OTf) tested, Ag(OTf) was found to be the best catalyst, but the yield and diastereoselectivity of the target compound **3a** were moderate (Table 1, entries 1–3). With the hope of increasing the yield and diastereoselectivity, we tried the reaction by increasing the catalyst loading from 10 to 20 mol % of Ag(OTf). However, there was no satisfactory increase in yield and diastereoselectivity (Table 1, entries 3 and 4). This indicates that Lewis acids are not efficient catalysts for the present S_N2 reaction. The MBH acetates **2** were obtained by acetylation of the corresponding MBH adducts with acetyl chloride in the presence of pyridine in dichloromethane as reported earlier by Basavaiah et al.[15]

Table 1
Optimization of reaction conditions for the formation of representative intermediate product **3a**[a]



2a **1** **3a**

Entry	Catalyst (mol %)	Solvent	Yield[b] (%)	*anti*:*syn*[c]
1	$FeCl_3$ (10)	CH_2Cl_2	35	51:49
2	$Cu(OTf)_2$(10)	CH_2Cl_2	38	58:42
3	Ag(OTf) (10)	CH_2Cl_2	41	63:37
4	Ag(OTf) (20)	CH_2Cl_2	48	63:37
5	PPh_3 (20)	THF–H_2O (2:1)	67	69:31
6	3-QDL (20)	THF–H_2O (2:1)	63	73:27
7	DABCO (20)	THF–H_2O (2:1)	90	95:5
8	DABCO (20)	MeOH–H_2O (2:1)	77	80:20
9	DABCO (20)	1,4-Dioxane–H_2O (2:1)	73	84:16
10	DABCO (15)	THF–H_2O (2:1)	81	82:18
11	DABCO (25)	THF–H_2O (2:1)	90	95:5
12	—	THF–H_2O (2:1)	—	—

[a] For the experimental procedure, see Ref. 16.
[b] Yield of isolated and purified products.
[c] As determined by ^1H NMR spectroscopy of the crude products.

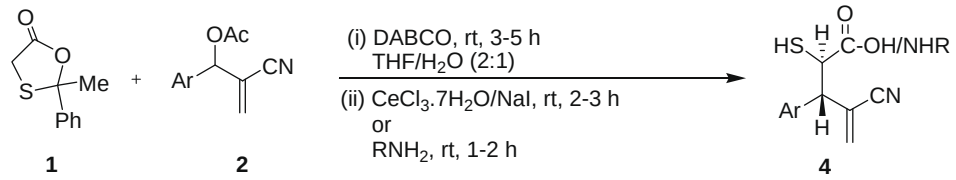
Then, we turned our attention to use a base catalyst for the present reaction and found that amongst 1,4-diazabicyclo[2.2.2]octane (DABCO), 3-quinclidinol (3-QDL), and triphenylphosphine (PPh_3), DABCO gave the best result in terms of the yield and diastereoselectivity (Table 1, entry 7).[16] This is in conformity with the earlier reports on DABCO-catalyzed direct nucleophilic substitution at α-position of MBH acetates via S_N2'–S_N2' mechanism.[1i] The optimum catalyst loading for DABCO was found to be 20 mol %. When the amount of the catalyst decreased to 15 mol % from 20 mol % relative to substrates, the yield and diastereoselectivity of **3a** reduced (Table 1, entries 7 and 10), but on using 25 mol % of the catalyst, no effect on yield and diastereoselectivity was observed (Table 1, entries 7 and 11). However, the reaction did not occur in the absence of a catalyst (Table 1, entry 12). Optimization of the solvents for the synthesis of **3a** in the presence of DABCO, was also undertaken and it was found that amongst THF/H_2O (2:1), MeOH/H_2O (2:1), and 1,4-dioxane/H_2O (2:1), the best solvent in terms of yield and diastereoselectivity was THF/H_2O (2:1) (Table 1, entries 7–9). It was noted that a higher reaction temperature, for example, in a refluxing solvent instead of at rt, led to decreased diastereoselectivity without any appreciable effect on the yield.

The present optimized synthesis is accomplished by stirring a mixture 2-methyl-2-phenyl-1,3-oxathiolan-5-one **1**, MBH acetate **2**, and DABCO (20 mol %) in THF/H_2O (2:1) at rt for 3–5 h. The products **3** thus formed were in situ subjected to $CeCl_3$/NaI·$7H_2O$-catalyzed selective hydrolysis of the 1,3-oxathiolan-5-one ring or its aminolysis with RNH_2 to afford the target compounds **4a–c**[17] and **4d–l**,[18] respectively (Table 2). In order to investigate the scope of the substrate for general validity of the present investigation, several MBH acetates **2** and NH_3/amines (RNH_2) were used employing the present optimized reaction conditions (Table 2). The yields and diastereoselectivities were found to be consistently good (Table 2), the highest yield (94%) and the best *anti*-diastereoselectivity (99%) were in the case of compound **4i** (Table 2, entry 9). Isolation and purification by recrystallization afforded hitherto unknown target compounds **4** in 83–94% yield with 95–99% diastereoselectivity in favor of the *anti*-isomer (Table 2).

The diastereomeric ratios in the crude isolates were checked by ^1H NMR spectroscopy to note any alteration of these ratios during subsequent purification. The crude isolates of **4** were found to be a diastereomeric mixture containing 92–96% of the *anti*-isomer. On the basis of ^1H NMR spectroscopy and the literature precedent,[1j,11e] the *anti*-stereochemistry was conclusively assigned to **3** and **4**, as their coupling constant ($J_{SCH,ArCH}$ = 11.4–11.8 Hz) was greater than that for the minor *syn*-isomer ($J_{SCH,ArCH}$ = 3.8–3.9 Hz). The coupling constants for vicinal protons of the analogous *anti*-diastereomers are reported to be J = 11.3–12.0 Hz,[1j,11e] which are comparable to that of compounds **3** and **4** and thus confirming their *anti*-stereochemistry. The transition state leading to the formation of the product **3** adopts the most stable *anti*-configuration about the ensuing C–C bond at α-position of MBH acetate **2**. Thus, compounds **3** are formed with high *anti*-diastereoselectivity, which is also retained in **4** as the chiral carbons of **3** incorporated in products **4** are not involved in any bond breaking/formation (Scheme 2).

The formation of compounds **4** may be explained by the tandem S_N2'–S_N2' reaction[1j,2a,11,12] of MBH acetate **2** with DABCO and 2-methyl-2-phenyl-1,3-oxathiolan-5-one **1** followed by H_2O/RNH_2-driven mercaptoacetylative ring opening of the resulting **3** to afford the target compounds **4** as depicted in Schemes 2 and 3. The acetophenone formed as by-product, was easily recovered and reused for the preparation of mercaptoacetyl transfer agent, 2-methyl-2- phenyl-1,3-oxathiolan-5-one **1** by treating with LiBr and mercaptoacetic acid (Scheme 2).

Table 2
One-pot synthesis of compounds **4** from MBH acetates **2**



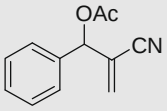
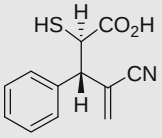
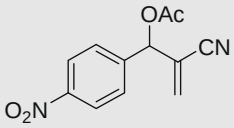
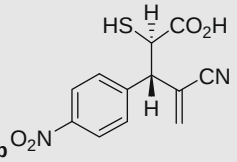
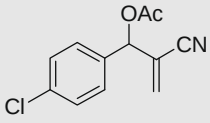
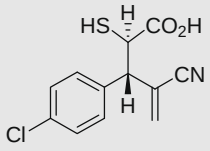
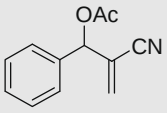
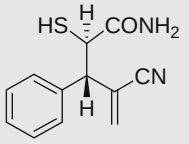
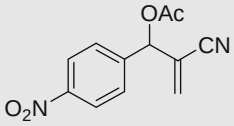
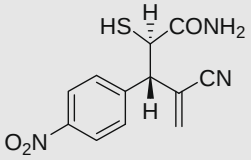
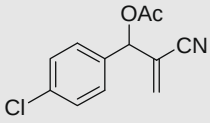
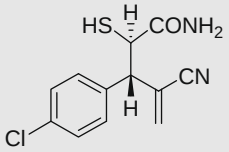
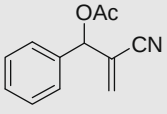
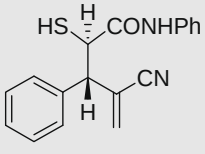
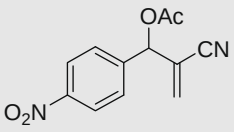
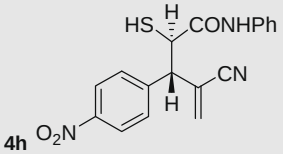
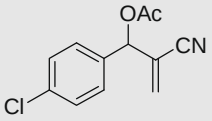
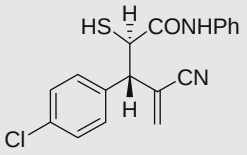
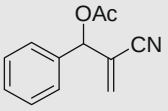
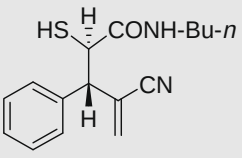
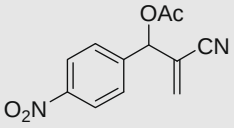
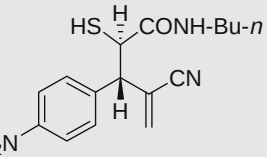
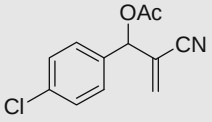
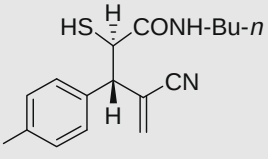
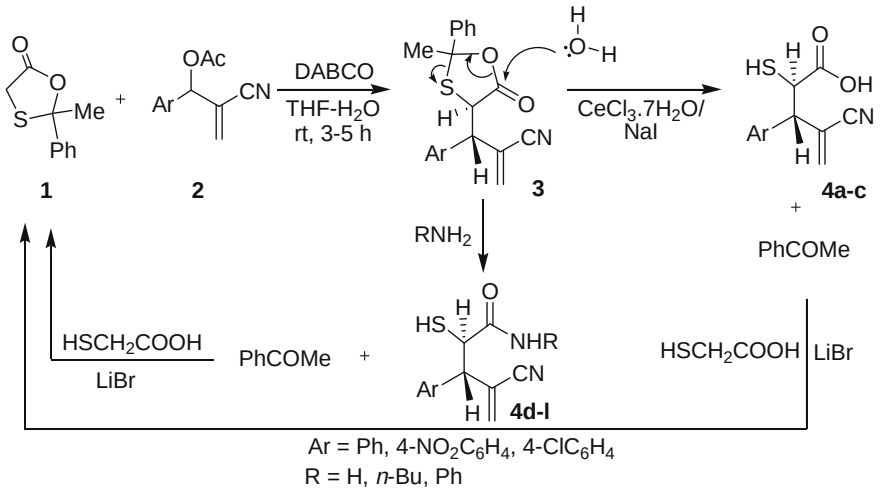
Entry	MBH acetate **2**	Time[a] (h)	Product	Yield[b,c] (%)	*anti*:*syn*[d]
1		8	 **4a**	84	95:5
2		6	 **4b**	90	95:5
3		7	 **4c**	93	98:2
4		7	 **4d**	91	95:5
5		7	 **4e**	83	99:1
6		6	 **4f**	91	98:2
7		6	 **4g**	91	97:3

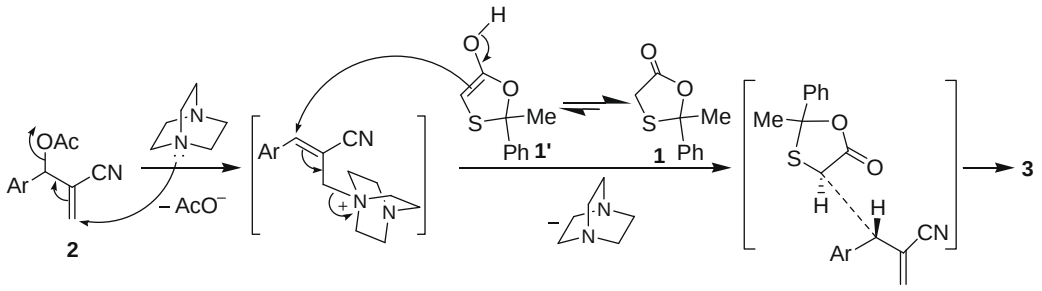
Table 2 (*continued*)

Entry	MBH acetate **2**	Time[a] (h)	Product	Yield[b,c] (%)	*anti*:*syn*[d]
8		6	 **4h**	92	96:4
9		7	 **4i**	94	99:1
10		7	 **4j**	89	98:2
11		6	 **4k**	93	95:5
12		7	 **4l**	92	97:3

[a] Total stirring time at rt for completion of both the steps (i) and (ii).
[b] Yield of isolated and purified products.
[c] All compounds gave C, H, and N analyses ±0.37% and satisfactory spectral (IR, ^{1}H NMR, ^{13}NMR, and EI-MS) data.
[d] As determined by ^{1}H NMR spectroscopy of the crude products.



Scheme 2. Formation of MBH acetate-derived α-mercapto acids/amides **4** and recycling of acetophenone formed as by-product.



Scheme 3. Plausible mechanism for the DABCO-catalyzed formation of product **3** from **2**.

In summary, we have demonstrated for the first time a direct introduction of α-mercaptoacetic acid/amide units into MBH acetates leading to the products of high synthetic importance with several diversity points. Thus, the present protocol opens up a new aspect for the utility of MBH adducts.

Acknowledgment

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References and notes

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16. *Isolation of intermediate* ***3a*** *and its conversion into the corresponding acid* ***4a*** *and amide* ***4d***: To a well-stirred solution of MBH acetate **2** (2 mmol) in 15 mL of THF/H_2O (2:1, v/v), DABCO (0.4 mmol) was added and stirred for 30 min at rt followed by addition of 2-methyl-2-phenyl-1,3-oxathiolan-5-one **1** (2 mmol) and stirring at rt for 4.5 h (Table 1). After completion of the reaction as indicated by TLC, the solvent was evaporated under reduced pressure, water (15 mL) was added and the product was extracted with EtOAc (3 × 15 mL). The combined organic layer was washed with brine (25 mL), dried over magnesium sulfate, filtered, and evaporated to dryness. The crude product thus obtained was purified by column chromatography to afford an analytically pure sample of a single diastereomer **3a** (Table 1). The product **3a** (2 mmol) was dissolved in 10 mL of THF/H_2O (2:1, v/v), then $CeCl_3{\cdot}7H_2O$ (0.2 mmol) and NaI (0.2 mmol) were added and the reaction mixture was stirred at rt for 2 h. After completion of the reaction, water (10 mL) was added and the combined organic layer was extracted with CH_2Cl_2 (3 × 10 mL), concentrated under reduced pressure and the crude product **4a** thus obtained was recrystallized from ethanol to afford an analytically pure **4a**, quantitatively. Following the similar procedure as used for **4a**, we isolated the corresponding amide **4d**, quantitatively, except that in this case only NH_4OAc (2 mmol) was used instead of H_2O and $CeCl_3{\cdot}7H_2O$/NaI for **4a**. Physical data of isolated compound **3a**: yellowish solid, yield 90%, mp 203–205 °C. IR (KBr) ν_{max} 3045, 2219, 1772, 1603, 1585, 1459 cm^{-1}. ^1H NMR (400 MHz; $CDCl_3$/TMS) δ: 2.29 (s, 3H, Me), 4.13 (d, 1H, $J_{ArCH,SCH}$ = 11.4 Hz, SCH), 4.61 (d, 1H, $J_{ArCH,SCH}$ = 11.4 Hz, ArCH), 5.87 (s, 1H, =CH), 5.93 (s, 1H, =CH), 7.13–7.65 (m, $10H_{arom}$). ^{13}C NMR (100 MHz; $CDCl_3$/TMS) δ: 35.1, 40.8, 51.2, 64.3, 117.1, 123.8, 125.6, 126.3, 127.2, 128.0, 129.3, 130.1, 131.3, 132.0, 132.8, 172.6. EIMS (*m/z*): 335 (M^+). Anal. Calcd for $C_{20}H_{17}NO_2S$: C, 71.62; H, 5.11; N, 4.18. Found: C, 71.37; H, 5.48; N, 4.41.
17. *General procedure for the one-pot synthesis of α-mercapto acids* ***4a–c***: The MBH acetate **2** (2 mmol) was dissolved in 15 mL of THF/H_2O (2:1, v/v) and DABCO (0.4 mmol) was added to it, the reaction mixture was stirred for 30 min at rt. Thereafter, 2 mmol of 2-methyl-2-phenyl-1,3-oxathiolan-5-one **1** was added to the reaction mixture and it was stirred for the next 3–5 h at rt (Table 2). After completion of the reaction, as indicated by TLC, $CeCl_3{\cdot}7H_2O$ (0.2 mmol) and NaI (0.2 mmol) were added and the reaction mixture was stirred for the next 2–3 h at rt. The solvent was evaporated under reduced pressure, water (15 mL) was added and extracted with CH_2Cl_2 (3 × 15 mL), the combined organic phase was concentrated under reduced pressure and the crude product **4a**, thus obtained was recrystallized from ethanol to afford a diastereomeric mixture (>94:<6; in the crude products the ratio was >91:<9 as determined by ^1H NMR spectroscopy). The product on second recrystallization from ethanol furnished an analytically pure sample of a single diastereomer **4** (Table 2). On the basis of comparison of *J* values to the literature ones,[1j,11e] the *anti*-stereochemistry was assigned to **4**, as the coupling constant ($J_{2H,3H}$ = 11.4–11.8 Hz) for **4** was higher than that for very minor (<6%) diastereomer (*syn*), $J_{2H,3H}$ = 3.8–3.9 Hz. Physical data of representative compound **4a**: Yellowish solid, yield 84%, mp 165–167 °C. IR (KBr) ν_{max} 3351–2658, 3041, 2556, 2221, 1675, 1602, 1579, 1451 cm^{-1}. ^1H NMR (400 MHz; $CDCl_3$/TMS) δ: 1.62 (d, 1H, $J_{ArCH,SCH}$ = 7.8 Hz, SH, exchangeable with D_2O), 3.88 (dd, 1H, $J_{ArCH,SCH}$ = 7.8, $J_{ArCH,SCH}$ = 11.8 Hz, 2-H), 4.15 (d, 1H, $J_{ArCH,SCH}$ = 11.8 Hz, 3-H), 5.85 (s, 1H, =CH), 5.97 (s, 1H, =CH), 7.09–7.51 (m, $5H_{arom}$), 11.23 (br s, 1H, exchangeable with D_2O). ^{13}C NMR (100 MHz; $CDCl_3$/TMS) δ: 40.5, 46.8, 117.2, 123.5, 126.5, 128.8, 129.5, 131.2, 132.9, 174.2. EIMS (*m/z*): 233 (M^+). Anal. Calcd for $C_{12}H_{11}NO_2S$: C, 61.78; H, 4.75; N, 6.00. Found: C, 62.05; H, 4.49; N, 6.37.
18. *General procedure for the one-pot synthesis of α-mercapto amides* ***4d–l***: The procedure followed was the same as described above for the synthesis of **4a–c** (Ref. 15) except that NH_4OAc (2 mmol) or an amine (2 mmol) was used instead of H_2O and $CeCl_3{\cdot}7H_2O$/NaI. Reaction time, yield, and diastereoselectivity for compounds **4** are given in Table 2. The crude product obtained was recrystallized from ethanol. To obtain analytically pure sample of a single diastereomer and to assign the stereochemistry of **4d–l**, the same procedure was adopted as described above (Ref. 17) for **4a–c**. The crude product in this case was found to be a diastereomeric mixture containing 92–96% of the *anti*-isomer as determined by ^1H NMR spectroscopy. Physical data of representative

compounds. Compound **4d**: yellowish solid, yield 91%, mp 142–144 °C. IR (KBr) ν_{max} 3450, 3057, 2553, 2218, 1679, 1599, 1585, 1453 cm^{-1}. ^1H NMR (400 MHz; $CDCl_3$/TMS) δ: 1.59 (d, 1H, $J_{ArCH,SCH}$ = 7.8 Hz, SH, exchangeable with D_2O), 3.97 (dd, 1H, $J_{ArCH,SCH}$ = 7.8, $J_{ArCH,SCH}$ = 11.5 Hz, 2-H), 4.03 (d, 1H, $J_{ArCH,SCH}$ = 11.5 Hz, 3-H), 5.79 (s, 1H, =CH), 5.96 (s, 1H, =CH), 6.18 (br s, 2H, NH, exchangeable with D_2O), 7.13–7.59 (m, $5H_{arom}$). ^{13}C NMR (100 MHz; $CDCl_3$/TMS) δ: 42.1, 46.9, 117.2, 123.3, 126.8, 127.8, 128.5, 129.9, 132.7, 172.5. EIMS (*m*/*z*): 232 (M^+). Anal. Calcd for $C_{12}H_{12}N_2OS$: C, 62.04; H, 5.21; N, 12.06. Found: C, 61.67; H, 5.56; N, 11.83. Compound **4i**: Yellowish solid, yield 94%, mp 179–181 °C. IR (KBr) ν_{max} 3449, 3058, 2555, 2227, 1658, 1608, 1576, 1457 cm^{-1}. ^1H NMR (400 MHz; $CDCl_3$/TMS) δ: 1.61 (d, 1H, $J_{ArCH,SCH}$ = 7.5 Hz, SH, exchangeable with D_2O), 3.94 (dd, 1H, $J_{ArCH,SCH}$ = 7.5, $J_{ArCH,SCH}$ = 11.8 Hz, 2-H), 4.08 (d, 1H, $J_{ArCH,SCH}$ = 11.8 Hz, 3-H), 5.81 (s, 1H, =CH), 5.98 (s, 1H, =CH), 7.11–7.48 (m, $7H_{arom}$), 7.61–7.85 (m, $2H_{arom}$), 8.23 (br s, 1H, NH, exchangeable with D_2O). ^{13}C NMR (100 MHz; $CDCl_3$/TMS) δ: 41.9, 47.2, 117.7, 123.1, 126.2, 127.0, 127.9, 128.5, 129.3, 130.1, 130.7, 131.5, 132.3, 174.2. EIMS (*m*/*z*): 342, 344 (M, M+2). Anal. Calcd for $C_{18}H_{15}ClN_2OS$: C, 63.06; H, 4.41; N, 8.17. Found: C, 63.29; H, 4.73; N, 7.89.