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Elimination of benzotriazolyl group in *N*-(α-benzotriazol-1-ylalkyl)amides and *N*-(α-benzotriazol-1-ylalkyl)sulfonamides: their self-coupling and cross-coupling reactions with carbonyl compounds

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Abstract—The elimination of benzotriazolyl group from *N*-(α-benzotriazol-1-ylalkyl)amides and *N*-(α-benzotriazol-1-ylalkyl)sulfonamides are readily realized with samarium diiodide as a reducing agent. The resulting intermediates undergo a dimerization or cross-coupling reaction with carbonyl compounds, thus affording the corresponding dimers or α-hydroxyalkylated sulfonamides in moderate yields.

1. Introduction

Benzotriazole is a very useful synthetic auxiliary[1] and its application in organic chemistry has been extensively investigated. One of the most important aspects of benzotriazole chemistry is its elimination at the appropriate stage.[1e] Several methods have been exploited for the removal of the benzotriazole group and reduction is often indispensable. The single-electron reducing agent SmI_2 is well known for its subtle reductivity and has been widely used in reductive coupling reactions.[2] It has been reported that SmI_2 is capable of eliminating the benzotriazole group in several cases.[3] For example, SmI_2 can remove the benzotriazolyl moiety from α-benzotriazolyl ketones to afford the corresponding ketones[3a] and from *N*-acylbenzotriazoles to give α-diketones.[3b] Also, SmI_2 causes the smooth elimination of benzotriazoyl radical (Bt˙) from *N*-[(*N*′,*N*′-dialkylamino)alkyl]benzotriazoles and thus affords the tertiary vicinal diamines.[3c] Furthermore, SmI_2 can eliminate the Bt˙ unit from appropriately designed benzotriazole adducts with an activated double bond to produce an α-amino radical, which undergoes intramolecular addition to the double bond to afford *N*-cycloalkylamines.[3d] Therefore, it would be interesting to see whether further applications of SmI_2 chemistry on benzotrizole derivatives can be developed to bring about various functionalized compounds, which are otherwise inaccessible by conventional routes.

The fact that *N*-[(*N*′,*N*′-dialkylamino)alkyl]benzotriazoles are reactive towards SmI_2[3c] and the structural similarity of *N*-(α-benzotriazol-1-ylalkyl)amides (obtainable by the union of an amide, an aldehyde, and benzotriazole[4]) to *N*-[(*N*′,*N*′-dialkylamino)alkyl]benzotriazoles (the adducts obtained from an amine, an aldehyde, and benzotriazole[5]) make it reasonable to postulate that the benzotriazole group in *N*-(α-benzotriazol-1-ylalkyl)amides may be susceptible to SmI_2 reduction.

2. Results and discussion

2.1. SmI_2-promoted self-coupling of *N*-(α-benzotriazol-1-ylalkyl)amides and *N*-(α-benzotriazol-1-ylalkyl)sulfonamides

Just as anticipated, as shown in Scheme 1, the reductive dimerization of *N*-(α-benzotriazol-1-ylalkyl)amides occurred in the presence of SmI_2 to afford **2** in moderate to good yields.

As can be seen in Table 1, when R^2 is a phenyl group, both *N*-(α-benzotriazol-1-ylalkyl)amides derived from aromatic aldehydes and aliphatic aldehydes can afford smoothly the corresponding dimers (entries 1–5), which were reported to be formed from the irradiation of the difficult-to-obtain

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Keywords: samarium diiodide; reductive coupling; *N*-(α-benzotriazol-1-ylalkyl)amides; *N*-(α-benzotriazol-1-ylalkyl)sulfonamides.

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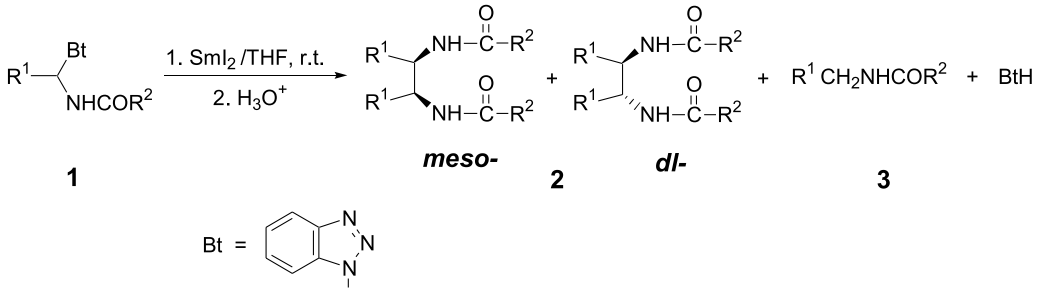
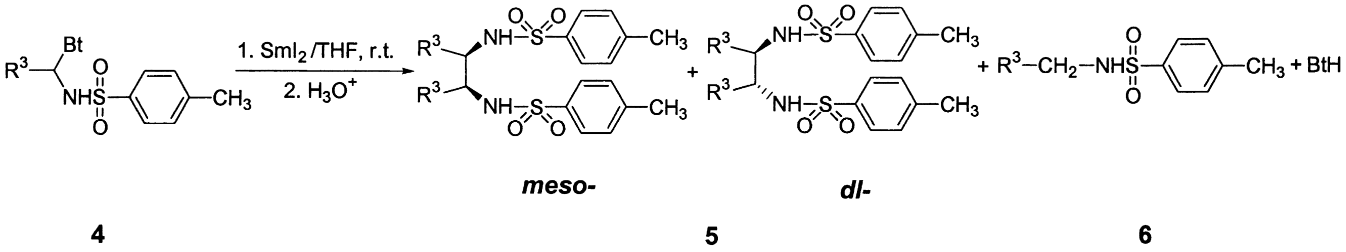


Scheme 1.

Table 1. SmI_2-promoted self-coupling of *N*-(α-benzotriazol-1-ylalkyl)amides

Entry	R^1	R^2	Product	Yield of **2** (%)	*meso*:*dl*[a] of **2**	Yield of **3** (%)
1	C_6H_5	C_6H_5	**2a**	65	67:33	28
2	4-$MeOC_6H_4$	C_6H_5	**2b**	62	75:25	22
3	*n*-Pr	C_6H_5	**2c**	70	96:4	21
4	*i*-Pr	C_6H_5	**2d**	68	65:35	21
5	*i*-Bu	C_6H_5	**2e**	76	100:0	17
6	C_6H_5	CH_3	**2f**	–	–	92

[a] The ratio was determined by 400 MHz ^{1}H NMR spectral data.



Scheme 2.

N-acylimines.[6] Aside from products **2**, the simple debenzotriazolation products **3** were isolated as by-products. It should be pointed out that when R^2 is a methyl, the simple reduction product **3** becomes the only product (entry 6).

In light of the above outcome, it seemed worthwhile to have an investigation on *N*-(α-benzotriazol-1-ylalkyl)sulfonamides[7] (compounds **4**), which are easily formed from sulfonamides, aldehydes and benzotriazole. At the outset, compound **4a** was added in the form of a saturated THF solution to the SmI_2-THF solution. It was found that the simple reduction product **6a** was the major product while the coupling product **5a** was obtained in a 30% yield (Scheme 2 and Table 2, entry 1). Since the solubility of substrate **4a** in THF is poor, we added solid **4a** instead, and surprising, the yield of **5a** was increased appreciably (Table 2, entry 2). However, for *N*-(α-benzotriazol-1-ylalkyl)sulfonamides derived from aliphatic aldehydes, only products **6** were obtained in nearly quantitative yields (Table 2, entries 4 and 5). The interpretation may be that the carbon radical resulting from the cleavage of C–Bt bond abstracts a hydrogen from THF[8a] more quickly than it dimerizes; or that the radical is further reduced to the carbanion which abstracts a proton from THF[8b] affording product **6** and failing to give the corresponding dimers **5**.

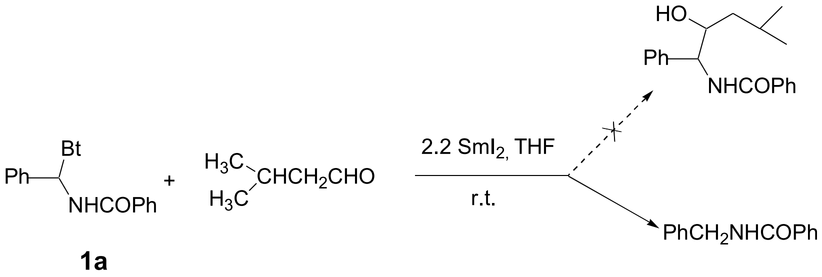
Table 2. SmI_2 promoted self-coupling of *N*-(α-benzotriazol-1-ylalkyl)sulfonamides

Entry	R^3	Product	Yield of **5** (%)	*meso*:*dl*[a] of **5**	Yield of **6** (%)
1	C_6H_5	**5a**	30[b]	>99:1	62
2	C_6H_5	**5a**	65[c]	>99:1	27
3	4-MeC_6H_4	**5b**	60	>99:1	22
4	*n*-Pr	**5c**	0	–	96
5	*i*-Pr	**5d**	0	–	94

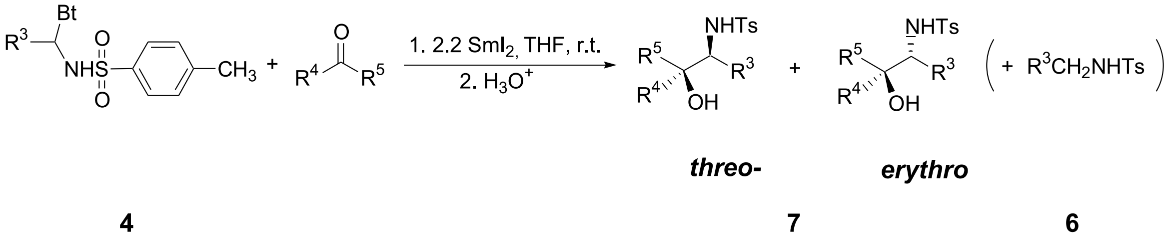
[a] The ratio was determined by 400 MHz ^{1}H NMR spectral data.
[b] A saturated solution of **4a** in THF was added to SmI_2 in THF.
[c] Solid **4a** was added to SmI_2 in THF.

2.2. SmI_2-promoted cross-coupling of *N*-(α-benzotriazol-1-ylalkyl)sulfonamides with carbonyl compounds

Intermolecular cross-coupling of carbonyl compounds with imines is an important way for the preparation of β-amino alcohols.[9] The reductive coupling reaction of oximes with carbonyl compounds affording β-alkoxyamino alcohols can be realized either by SmI_2[10a] or by electroreduction.[10b] SmI_2-promoted cross-coupling reaction between *N*-sulfonylimines and aldehydes with a ferrocene structure can give β-sulfonamido alcohols[11] in an enantioselective as well as diastereoselective manner. The protocols mentioned above for the synthesis of β-amino alcohols or their derivatives all involve the cross-coupling between C=N bonds and C=O



Scheme 3.



Scheme 4.

bonds. Among other methods for the construction of β-amino alcohol derivatives, lithiation of the C atom adjacent to the nitrogen in amine derivatives and subsequent nucleophilic attack to the carbonyl compounds is well documented.[12] Very recently, SmI_2-mediated cross-coupling reaction between α-heteroatom-substituted amides and carbonyl compounds offers a conceptually new strategy for the construction of β-acylamido alcohols (α-hydroxyalkylation reaction of amides). For example, in the presence of SmI_2, α-sulfur-substituted aromatic lactams can undergo tandem desulfurization and reductive coupling reactions with carbonyl compounds to afford the α-hydroxyalkylated lactams in satisfactory yields.[13] Furthermore, the SmI_2 promoted α-hydroxyalkylation reaction of amides is applied in the preparation of peptide libraries.[14a]

With our successful SmI_2-promoted debenzotriazolation protocol in hand, we investigated the cross-coupling reaction between *N*-(α-benzotriazol-1-ylalkyl)amides and carbonyl compounds to explore the α-hydroxyalkylation of amides.

Disappointingly, when **1a** and iso-valeraldehyde were tested, the expected α-hydroxyalkylated amides could not be obtained and only in high yields was obtained the simple reduction compound (Scheme 3). Further experiment was carried out to find out if the cross-coupling reaction between **4** and aldehydes could occur. It was gratifying to see that when a suspension of 1 mmol of **4a** dissolved in 10 mL THF was added slowly to a 20 mL THF solution of 2.2 equiv. of SmI_2 and 1 mmol of iso-butyraldehyde, a diastereoisomeric mixture of the α-hydroxyalkylated sulfonamides **7a** in 56% yield could be obtained. Also isolated from the reaction mixture was the simple reduction product **6** in 35% yield. Optimization of the reaction conditions led to the observation that excess amount of aldehydes could increase the yield of product **7a** from 56 to 73%, which was satisfactory considering the simplicity of the reaction conditions.

To explore the generality of this reaction, a series of aldehydes and ketones were subjected to the cross-coupling reaction with substrates **4a** or **4b** at the optimized conditions, and reasonable to good yields of products **7** were obtained (Scheme 4). Compound **4c** derived from aliphatic aldehydes, however, did not afford any cross-coupling product and only the simple reduction product **6** was obtained (Table 3, entry 13).

According to the literature,[11,14] a α-sulfonamido carbanion mechanism is strongly favored in this cross-coupling reaction, though in the absence of the carbonyl compounds under the SmI_2-THF conditions self-coupling of **4** likely involve a radical mechanism.

The *threo*:*erythro* selectivities, for the present reaction are shown in Table 3. The major products have larger coupling constants between CH–O and CH–N than that of the minor products, and the major products were assigned to be *threo*-based on literature precedents.[15] Though an in-depth mechanistic investigation of the cross-coupling reaction was not pursued, a tentative explanation of the preference of the *threo*- to the *erythro*-products is illustrated in Scheme 5.

Since lanthanides are oxophilic,[16] transition states T1 and T2 are likely involved. However, the sterically less cumbersome T2 would be more favorable as can be seen in Scheme 5. As for aldehydes, a more than 80:20 *threo*:*erythro* ratio of products **7** can always be obtained; as for the ketones, when R^4 and R^5 are comparable in bulkiness the selectivity vanishes (*threo*:*erythro*≈1:1, entries 4–6). On the other hand, when one of the alkyl groups in the ketone is substantially larger than the other, the *threo*-selectivity re-emerges (entries 7, 11).

In conclusion, the benzotriazole group in *N*-(α-benzotriazol-1-ylalkyl)amides or *N*-(α-benzotriazol-1-ylalkyl)sulfonamides can be eliminated by using SmI_2 as a reducing reagent. Subsequent self-coupling reaction affords the corresponding dimers in good yields. Besides, the cross-coupling reaction between *N*-(α-benzotriazol-1-ylalkyl)sulfonamides

Table 3. SmI_2-promoted stereoselective cross-coupling of *N*-(α-benzotriazol-1-ylalkyl)sulfonamides with carbonyl compounds

Entry	R^3	R^4	R^5	Product	*threo*:*erythro*[a]	Yield (%)[b] of **7**	Yield (%) of **6**
1	C_6H_5 (**4a**)	H	$(CH_3)_2CH$	**7a**	83:17	73	18
2	C_6H_5	H	$(CH_3)_2CHCH_2$	**7b**	90:10	71	22
3	C_6H_5	CH_3	CH_3	**7c**	–	78	16
4	C_6H_5	CH_3	CH_3CH_2	**7d**	50:50	71	22
5	C_6H_5	CH_3	$CH_3(CH_2)_2$	**7e**	53:47	68	26
6	C_6H_5	CH_3	$CH_3(CH_2)_3$	**7f**	53:47	69	22
7	C_6H_5	CH_3	$CH_3(CH_2)_4$	**7g**	72:28	65	32
8	C_6H_5	$-(CH_2)_4-$		**7h**	–	65	31
9	C_6H_5	$-(CH_2)_5-$		**7i**	–	62	34
10	$4\text{-}CH_3C_6H_4$ (**4b**)	CH_3	CH_3	**7j**	–	79	14
11	$4\text{-}CH_3C_6H_4$	CH_3	$(CH_3)_2CH$	**7k**	87:13	59	33
12	$4\text{-}CH_3C_6H_4$	H	$(CH_3)_2CH$	**7l**	80:20	71	25
13	$(CH_3)_2CH$ (**4c**)	$-(CH_2)_4-$		**7m**	–	0	94

[a] The diastereoselectivity was determined by 400 MHz ^1H NMR spectral data.

[b] One mmol of substrate **4** was treated with 2 equiv. of the corresponding carbonyl compounds and 2.2 equiv. of SmI_2. Isolated yields were based on substrates **4**.

and carbonyl compounds offers a synthetically useful method for the realization of α-hydroxyalkylation of sulfonamides.

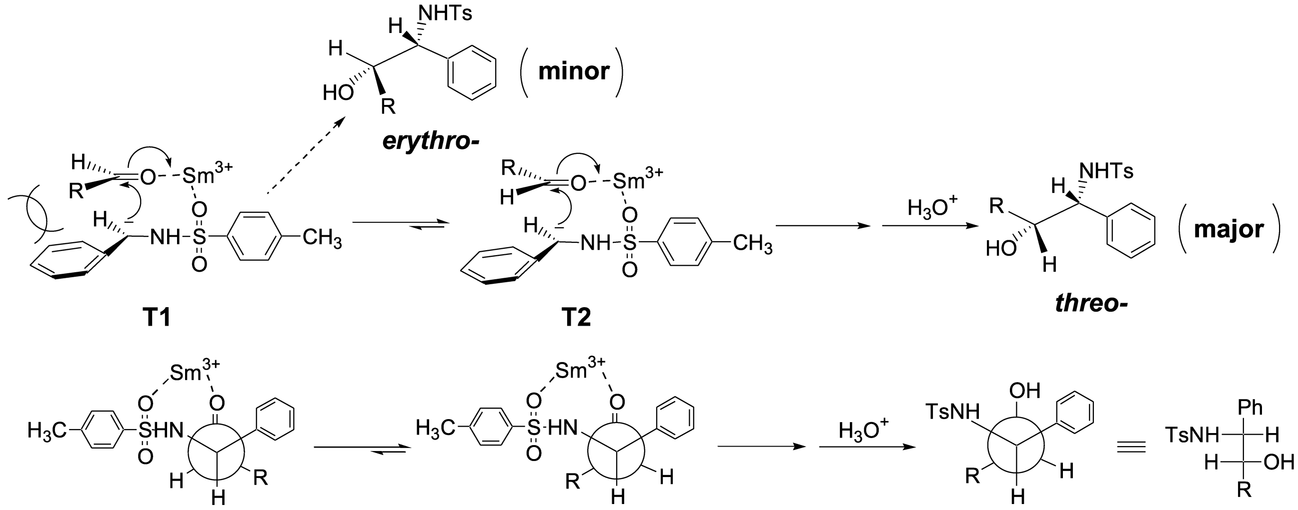
3. Experimental

3.1. General

Tetrahydrofuran was distilled from sodium-benzophenone and acetonitrile was distilled in the presence of phosphorus pentoxide immediately prior to use. All reactions were conducted under a nitrogen atmosphere. Melting points are uncorrected. ^1H NMR spectra were recorded on a Bruker AC-400 instrument using $CDCl_3$ or d^6-DMSO as solvent and TMS as internal standard. Chemical shifts (δ) are reported in ppm and coupling constants J are given in Hz. IR spectra were recorded using KBr disks with a Bruker Vector-22 infrared spectrometer. Mass spectra were recorded on a HP 5989B MS spectrometer. Elemental analyses were performed on an EA-1110 instrument. Metallic samarium and other reagents were purchased from commercial sources, without further purification before use. Substrates **1**[4] and **4**[7] were prepared according to literature procedures.

3.2. SmI_2-promoted self-coupling of *N*-(α-benzotriazol-1-ylalkyl)amides and *N*-(α-benzotriazol-1-ylalkyl)sulfonamides

Under nitrogen atmosphere, 1 mmol of *N*-(α-benzotriazol-1-ylalkyl)amides (**1**) dissolved in dry THF (5 mL) was added at room temperature to 2.2 mmol of SmI_2 dissolved in THF (20 mL). The resulting solution turned yellow in 20 min. Dilute hydrochloric acid (2 M, 5 mL) was added and the resulting mixture extracted with diethyl ether (3×20 mL). The combined organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was separated by preparative TLC on silica gel with ethyl acetate and cyclohexane (1:2) as eluent to afford the self-coupling products. For *N*-(α-benzotriazol-1-ylalkyl)sulfonamides (**4**), the operation was similar to that described above, except that solid *N*-(α-benzotriazol-1-ylalkyl)sulfonamides (**4**) was added to the SmI_2-THF solution.



Scheme 5.

3.3. SmI_2-promoted cross-coupling of *N*-(α-benzotriazol-1-ylalkyl)sulfonamides with carbonyl compounds

Under nitrogen atmosphere, 1 mmol of *N*-(α-benzotriazol-1-ylalkyl)sulfonamides (**4**) dissolved in dry THF (10 mL) was added at room temperature to a mixture of 2 mmol of carbonyl compound and 2.2 mmol of SmI_2 dissolved in THF (20 mL). The characteristic blue color of SmI_2 faded gradually with the addition of compound **4** in about 30 min. Dilute hydrochloric acid (2 M, 5 mL) was added and the resulting mixture extracted with diethyl ether (3×20 mL). The combined organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was separated by preparative TLC on silica gel with ethyl acetate and cyclohexane (1:2) as eluent to afford the α-hydroxyalkylated sulfonamides.

3.3.1. Compound 2a. The title compound was obtained as *meso*, white solid; mp >300°C (decomposition, lit.[6] 352°C). IR (KBr) ν_{max}: 3360 (NH), 3061, 3033, 1635, 1578, 1524 cm^{-1}. ^1H NMR (400 MHz, d_6-DMSO): δ 8.80 (2H, br, NH), 7.17–7.70 (20H, m, ArH), 5.67–5.69 (2H, m). *dl*, white solid; mp 292–295°C (lit.[6] 297°C). IR (KBr) ν_{max}: 3318 (NH), 3061, 3031, 1635, 1578, 1533 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.77 (4H, d, J=8.4 Hz), 7.38–7.49 (8H, m, ArH), 7.20–7.26 (10H, m, ArH), 5.59–5.61 (2H, m). *m*/*z* (%): 421 (M^++1, 0.26), 210 (34.48), 105 (100). $C_{28}H_{24}N_2O_2$. Calcd C, 79.98; H, 5.75; N, 6.66. Found C, 79.89; H, 5.74; N, 6.62%.

3.3.2. Compound 2b. The title compound was obtained as a *meso* and *dl* mixture, white solid. IR (KBr) ν_{max}: 3332 (NH), 3061, 2954, 2836, 1633, 1579, 1516 cm^{-1}. ^1H NMR (400 MHz, d_6-DMSO), *meso*: δ 8.71 (2H, br, NH), 7.36–7.61 (14H, m, ArH), 6.85 (4H, d, J=8.4 Hz), 5.59–5.61 (2H, m), 3.68 (6H, s). *dl*: δ 8.94 (2H, br, NH), 7.73 (4H, d, J=8.0 Hz, ArH), 7.36–7.61 (6H, m), 7.28 (4H, d, J=8.4 Hz), 6.79 (4H, d, J=8.8 Hz), 5.55–5.57 (2H, m), 3.68 (6H, s). *m*/*z* (%): 240 (M^+/2, 37.55), 105 (100). $C_{30}H_{28}N_2O_4$. Calcd C, 74.98; H, 5.87; N, 5.83. Found C, 74.91; H, 5.89; N, 5.78%.

3.3.3. Compound 2c. The title compound was obtained as a *meso* and *dl* mixture, white solid. IR (KBr) ν_{max}: 3336 (NH), 2957, 2871, 1634, 1579, 1534 cm^{-1}, *meso*: ^1H NMR (400 MHz, d_6-DMSO), δ 8.06 (2H, br, NH), 7.81–7.83 (4H, m, ArH), 7.45–7.52 (6H, m), 4.20–4.22 (2H, m), 1.49–1.52 (4H, m), 1.30–1.37 (4H, m), 0.86–0.88 (6H, m). *m*/*z* (%): 353 (M^++1, 0.24), 176 (10.26), 177 (24.10), 148 (7.29), 105 (100). $C_{22}H_{28}N_2O_2$. Calcd C, 74.97; H, 8.01; N, 7.95. Found C, 74.90; H, 8.10; N, 7.88%.

3.3.4. Compound 2d. The title compound was obtained as a *meso* and *dl* mixture, white solid. IR (KBr) ν_{max}: 3317 (NH), 3064, 2960, 1636, 1579, 1534 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$), *meso*: δ 7.69–7.72 (4H, m, ArH), 7.44–7.58 (2H, m, ArH), 7.36–7.40 (4H, m), 6.64 (2H, d, br, J=7.2 Hz), 4.16–4.19 (2H, m), 2.10–2.17 (2H, m), 1.04–1.08 (12H, t, J=7.2 Hz). *dl*: δ 7.83–7.86 (4H, m, ArH), 7.44–7.58 (6H, m, ArH), 6.32 (2H, d, br, J=6.8 Hz), 4.29–4.31 (2H, m), 2.06–2.08 (2H, m), 1.01–1.04 (12H, m). *m*/*z* (%): 353 (M^++1, 0.39), 176 (22.39), 177 (39.01), 162 (13.36), 105 (100). $C_{22}H_{28}N_2O_2$. Calcd C, 74.97; H, 8.01; N, 7.95. Found C, 74.90; H, 8.07; N, 7.90%.

3.3.5. Compound 2e. The title compound was obtained as *meso*. IR (KBr) ν_{max}: 3339 (NH), 3062, 2955, 2922, 2870, 1636, 1579, 1535 cm^{-1}. ^1H NMR (400 MHz, d_6-DMSO), δ 8.18 (2H, br, NH), 7.84–7.88 (4H, m, ArH), 7.44–7.52 (6H, m), 4.20 (2H, m), 1.53–1.57 (4H, m), 1.28–1.36 (2H, m), 0.65–0.71 (12H, m). *m*/*z* (%): 381 (M^++1, 0.57), 191 (32.24), 190 (17.01), 148 (28.65), 105 (100). $C_{24}H_{32}N_2O_2$. Calcd C, 75.75; H, 8.48; N, 7.36. Found C, 75.79; H, 8.54; N, 7.32%.

3.3.6. Compound 5a. The title compound was obtained as *meso*. IR (KBr) ν_{max}: 3316 (NH), 3031, 1599, 1456, 1327 cm^{-1}. ^1H NMR (400 MHz, d_6-DMSO), δ 8.14 (2H, d, J=9.2 Hz, NH), 7.19 (4H, d, J=8.0 Hz, ArH), 6.84–6.98 (14H, m), 4.51–4.53 (2H, m), 2.22 (6H, s). *m*/*z* (%): 260 (M^+/2, 90.15), 155 (56.24), 106 (47.61), 91 (100). $C_{28}H_{28}N_2O_4S_2$. Calcd C, 64.59; H, 5.42; N, 5.38. Found C, 64.68; H, 5.40; N, 5.31%.

3.3.7. Compound 5b. The title compound was obtained as *meso*. IR (KBr) ν_{max}: 3314 (NH), 3031, 2923, 1598, 1449, 1322 cm^{-1}, *meso*: ^1H NMR (400 MHz, $CDCl_3$), δ 7.49–7.53 (4H, m, ArH), 7.09 (4H, d, J=8.4 Hz, ArH), 6.78 (4H, d, J=8.4 Hz, ArH), 6.57–6.62 (4H, m, ArH), 5.67 (2H, br), 4.50–4.51 (2H, m), 2.36 (6H, s), 2.20 (6H, s). *m*/*z* (%): 549 (M^++1, 0.13), 274 (M^+/2, 70.64), 155 (34.22), 120 (67.12), 91 (100). $C_{30}H_{32}N_2O_4S_2$. Calcd C, 65.67; H, 5.88; N, 5.11. Found C, 65.62; H, 5.94; N, 5.13%.

3.3.8. Compound 7a. The title compound was obtained as an inseparable diastereoisomeric mixture, white solid. IR (KBr) ν_{max}: 3475 (OH), 3280 (NH), 2962, 2873, 1599, 1455, 1324, 1159 cm^{-1}. Major: ^1H NMR (400 MHz, $CDCl_3$): δ 7.49–7.53 (2H, m, ArH), 7.14–7.19 (3H, m, ArH), 7.02–7.10 (4H, m, ArH), 5.43 (1H, d, J=7.2 Hz, NH), 4.48 (1H, dd, J=4.8, 7.6 Hz, *CH*NH), 3.37–4.00 (1H, m), 2.35 (3H, s, CH_3), 1.88 (1H, br, OH), 1.66–1.87 (1H, m), 0.88–1.01 (6H, m). *m*/*z* (%): 260 (M^+−73, 33.53), 178 (6.95), 155 (24.86), 106 (100), 91 (53.55). Anal. $C_{18}H_{23}NO_3S$. Calcd C, 64.84; H, 6.95; N, 4.20. Found C, 64.92; H, 7.11; N, 4.17%.

3.3.9. Compound 7b. The title compound was obtained as an inseparable diastereoisomeric mixture, white solid. IR (KBr) ν_{max}: 3498 (OH), 3309 (NH), 2951, 2866, 1599, 1455, 1321, 1159 cm^{-1}. Major: ^1H NMR (400 MHz, $CDCl_3$): δ 7.52–7.54 (2H, m, ArH), 7.03–7.22 (7H, m, ArH), 5.44 (1H, d, J=8.0 Hz, NH), 4.29 (1H, dd, J=4.0, 8.0 Hz, *CH*NH), 3.92–3.98 (1H, m), 2.35 (3H, s, CH_3), 1.63–1.71 (1H, m), 1.53 (1H, br), 1.06–1.13 (1H, m), 0.95–1.02 (1H, m), 0.79–0.87 (6H, m). *m*/*z* (%): 330 (M^+−17, 0.21), 260 (20.93), 155 (17.19), 106 (100), 91 (53.45). Anal. $C_{19}H_{25}NO_3S$. Calcd C, 65.68; H, 7.25; N, 4.03. Found C, 65.59; H, 7.28; N, 4.01%.

3.3.10. Compound 7c. The title compound was obtained as white solid; mp 162–165°C. IR (KBr) ν_{max}: 3532 (OH), 3286 (NH), 3046, 2977, 2932, 1600, 1497, 1456, 1420 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.43–7.46 (2H, m, ArH), 7.09–7.17 (3H, m, ArH), 7.00–7.03 (4H, m, ArH), 5.50 (1H, d, J=8.4 Hz, NH), 4.17 (1H, d, J=8.8 Hz, *CH*NH), 2.31 (3H, s, CH_3), 1.62 (1H, br), 1.35 (3H, s), 1.03 (3H, s). *m/z* (%): 320 (M^++1, 1.04), 302 (35.62), 260 (2.99), 106 (100), 91 (18.25). Anal. $C_{17}H_{21}NO_3S$. Calcd C, 63.92; H, 6.63; N, 4.38. Found C, 64.01; H, 6.59; N, 4.35%.

3.3.11. Compound 7d. The title compound was obtained as an inseparable diastereoisomeric mixture, white solid. IR (KBr) ν_{max}: 3521 (OH), 3290 (NH), 3065, 2971, 2939, 1597, 1497, 1456, 1418, 1320 cm^{-1}. Major isomer: δ 7.41 (2H, d, J=8.0 Hz, ArH), 7.06–7.13 (3H, m, ArH), 6.97–7.02 (4H, m, ArH), 5.39–5.42 (1H, m, NH), 4.24 (1H, d, J=8.4 Hz, *CH*NH), 2.30 (3H, s, CH_3), 1.62–1.76 (2H, m), δ 1.49 (1H, s, *OH*), 0.92 (3H, s, COH*CH*$_3$), 0.97 (3H, t, J=7.6 Hz, *CH*$_3$CH$_2$). Minor isomer: δ 7.41 (2H, d, J=8.0 Hz, ArH), 7.06–7.13 (3H, m, ArH), 6.97–7.02 (4H, m, ArH), 5.39–5.42 (1H, m, NH), 4.22 (1H, d, J=8.8 Hz, *CH*NH), 2.30 (3H, s, CH_3), 1.42 (1H, s, *OH*), 1.33 (3H, s, COH*CH*$_3$), 1.20–1.26 (2H, m), 0.87 (3H, t, J=8.0 Hz, *CH*$_3$CH$_2$). *m/z* (%): 316 (M^+−17, 0.70), 260 (2.71), 155 (6.25), 106 (100), 91 (33.18), 73 (74.05). Anal. $C_{18}H_{23}NO_3S$. Calcd C, 64.84; H, 6.95; N, 4.20. Found C, 64.92; H, 6.91; N, 4.17%.

3.3.12. Compound 7e. The title compound was obtained as an inseparable diastereoisomeric mixture, white solid. IR (KBr) ν_{max}: 3499 (OH), 3276 (NH), 3034, 2959, 2872, 1599, 1497, 1457, 1423, 1327 cm^{-1}. ^1H NMR (400 MHz, d_6-DMSO), major isomer: δ 7.77 (1H, d, J=9.6 Hz, NH), 7.38 (2H, d, J=8.4 Hz), 7.01–7.12 (7H, m, ArH), 4.24 (1H, s, OH), 4.07 (1H, d, J=9.6 Hz, *CH*NH), 2.24 (3H, s, CH_3), 1.19–1.33 (4H, m), 0.80 (3H, s), 0.78 (3H, t, J=7.2 Hz). Minor isomer: δ 7.87 (1H, d, J=10 Hz, NH), 7.37 (2H, d, J=8.0 Hz), 7.01–7.12 (7H, m, ArH), 4.20 (1H, s, OH), 4.08 (1H, d, J=10 Hz, *CH*NH), 2.24 (3H, s, CH_3), 1.19–1.33 (4H, m), 0.97 (3H, s), 0.73 (3H, t, J=7.6 Hz). *m/z* (%): 330 (M^+−17, 0.72), 260 (2.26), 155 (6.25), 106 (100), 91 (35.36), 87 (62.01). Anal. $C_{19}H_{25}NO_3S$. Calcd C, 65.68; H, 7.25; N, 4.03. Found C, 65.76; H, 7.29; N, 4.07%.

3.3.13. Compound 7f. The title compound was obtained as an inseparable diastereoisomeric mixture, white solid. IR (KBr) ν_{max}: 3565, 3475 (OH), 3275 (NH), 3065, 2954, 2871, 1599, 1497, 1457, 1431, 1379 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$), major isomer: δ 7.40–7.43 (2H, dd, J=8.0, 8.4 Hz, ArH), 7.08–7.15 (3H, m, ArH), 6.98–7.02 (4H, m, ArH), 5.39–5.42 (1H, m, NH), 4.21 (1H, d, J=9.6 Hz, *CH*NH), 2.30 (3H, s, CH_3), 1.46 (1H, s, OH), 1.26–1.33 (2H, m), 1.14–1.19 (4H, m), 1.34 (3H, s), 0.82 (3H, t, J=7.6 Hz). Minor isomer: δ 7.40–7.43 (2H, dd, J=8.0, 8.4 Hz, ArH), 7.08–7.15 (3H, m, ArH), 6.98–7.02 (4H, m, ArH), 5.39–5.42 (1H, m, NH), 4.21 (1H, d, J=9.6 Hz, *CH*NH), 2.31 (3H, s, CH_3), 1.58–1.66 (2H, m), 1.50 (1H, s, OH), 0.92 (3H, s), 1.26–1.33 (4H, m), 0.90–0.94 (3H, m). *m/z* (%): 344 (M^+−17, 2.35), 260 (1.72), 155 (4.02), 106 (100), 101 (48.35), 91 (24.67). Anal. $C_{20}H_{27}NO_3S$. Calcd C, 66.45; H, 7.53; N, 3.87. Found C, 66.52; H, 7.57; N, 3.84%.

3.3.14. Compound 7g. The title compound was obtained as an inseparable diastereoisomeric mixture, white solid. IR (KBr) ν_{max}: 3562, 3416 (OH), 3257 (NH), 2949, 2868, 1599, 1497, 1459, 1388, 1322 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$), major isomer: δ 7.39–7.43 (2H, m, ArH), 7.08–7.16 (3H, m, ArH), 6.98–7.02 (4H, m, ArH), 5.40–5.45 (1H, m, NH), 4.21 (1H, d, J=8.8 Hz, *CH*NH), 2.30 (3H, s, CH_3), 1.45 (1H, s, OH), 1.33 (3H, s), 1.09–1.36 (8H, m), 0.84 (3H, t, J=7.6 Hz). Minor isomer: δ 7.39–7.43 (2H, m, ArH), 7.08–7.16 (3H, m, ArH), 6.98–7.02 (4H, m, ArH), 5.40–5.45 (1H, m, NH), 4.21 (1H, d, J=8.8 Hz, *CH*NH), 2.31 (3H, s, CH_3), 1.50 (1H, s, OH), 1.20–1.24 (3H, m), 1.09–1.36 (8H, m), 0.92 (3H, s). *m/z* (%): 358 (M^+−17, 0.78), 260 (2.10), 155 (5.40), 115 (48.13), 106 (100), 91 (33.21). Anal. $C_{21}H_{29}NO_3S$. Calcd C, 67.17; H, 7.78; N, 3.73. Found C, 67.11; H, 7.83; N, 3.69%.

3.3.15. Compound 7h. The title compound was obtained as white solid; mp 148–152°C. IR (KBr) ν_{max}: 3526 (OH), 3288 (NH), 2961, 1599, 1454, 1422, 1322, 1159 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.44 (2H, d, J=8.4 Hz, ArH), 7.00–7.16 (7H, m, ArH), 5.63–5.58 (1H, br), 4.29 (1H, d, J=8.8 Hz, *CH*NH), 2.31 (3H, s, CH_3), 1.59–1.86 (7H, m), 1.38 (1H, s, OH), 1.05–1.14 (1H, m). *m/z* (%): 328 (M^+−17, 1.72), 260 (1.90), 155 (4.43), 106 (100), 91 (28.36), 85 (54.75). Anal. $C_{19}H_{23}NO_3S$. Calcd C, 66.06; H, 6.71; N, 4.05. Found C, 66.14; H, 6.76; N, 4.01%.

3.3.16. Compound 7i. The title compound was obtained as white solid; mp 142–145°C. IR (KBr) ν_{max}: 3509 (OH), 3293 (NH), 3062, 2931, 1598, 1454, 1422, 1320, 1152 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.41 (2H, d, J=8.4 Hz, ArH), 7.08–7.14 (3H, m, ArH). 6.98–7.02 (4H, m, ArH), 5.48 (1H, d, J=8.8 Hz, NH), 4.23 (1H, d, J=9.6 Hz, *CH*NH), 2.30 (3H, s, CH_3), 1.92–1.96 (1H, br, OH), 1.53–1.58 (4H, m), 1.40–1.47 (3H, m), 1.19–1.26 (2H, m), 1.06–1.09 (1H, m). *m/z* (%): 342 (M^+−17, 0.55), 260 (1.10), 155 (3.41), 106 (100), 99 (54.23). Anal. $C_{20}H_{25}NO_3S$. Calcd C, 66.82; H, 7.01; N, 3.90. Found C, 66.90; H, 7.10; N, 3.83%.

3.3.17. Compound 7j. The title compound was obtained as white solid; mp 153–156°C. IR (KBr) ν_{max}: 3549 (OH), 3270 (NH), 3046, 2976, 2925, 1599, 1497, 1441, 1420, 1324, 1161 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.44 (2H, d, J=7.6 Hz, ArH), 7.03 (2H, d, J=8.0 Hz, ArH), 6.87–6.94 (4H, m, ArH), 5.38–5.46 (1H, br, NH), 4.13 (1H, d, J=8.8 Hz, *CH*NH), 2.33 (3H, s, CH_3), 2.27 (3H, s, CH_3), 1.64 (1H, br), 1.33 (3H, s), 1.04 (3H, s). *m/z* (%): 316 (M^+−17, 0.48), 274 (8.81), 155 (11.30), 120 (100), 91 (57.15). Anal. $C_{18}H_{23}NO_3S$. Calcd C, 64.84; H, 6.95; N, 4.20. Found C, 64.79; H, 6.91; N, 4.17%.

3.3.18. Compound 7k. The title compound was obtained as an inseparable diastereoisomeric mixture, white solid. IR (KBr) ν_{max}: 3499 (OH), 3278 (NH), 3039, 2981, 1598, 1497, 1448, 1425, 1320, 1153 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$), major isomer: δ 7.36 (2H, d, J=8.0 Hz, ArH), 6.96 (2H, d, J=7.6 Hz), 6.84–6.91 (4H, m, ArH), 5.36–5.41 (1H, br), 4.39 (1H, d, J=9.6 Hz, *CH*NH), 2.31 (3H, s, CH_3), 2.26 (3H, s, CH_3), 1.41 (1H, s, OH), 0.96–0.99 (6H, m), 0.84–0.87 (1H, m, $(CH_3)_2$*CH*), 0.75 (3H, s). Minor isomer: δ 7.50 (2H, d, J=8.4 Hz, ArH), 7.11 (2H, d, J=8.0 Hz), 6.84–6.91 (4H, m, ArH), 5.22–5.24 (1H, br), 4.53 (1H, d, J=8.4 Hz, *CH*NH), 2.37 (3H, s, CH_3), 2.29 (3H, s, CH_3), 1.42 (1H, s, OH), 1.28 (3H, s), 0.96–0.99 (6H, m), 0.89–0.94 (1H, m, $(CH_3)_2$*CH*). *m/z* (%): 274 (M^+−87, 3.87), 155 (6.17), 120 (100), 91 (40.56), 87 (58.23). $C_{20}H_{27}NO_3S$. Calcd C, 66.45; H, 7.53; N, 3.87. Found C, 66.51; H, 7.60; N, 3.82%.

3.3.19. Compound 7l. The title compound was obtained as an inseparable diastereoisomeric mixture, white solid. IR (KBr) ν_{max}: 3491 (OH), 3280 (NH), 2961, 2873, 1598, 1444, 1321, 1159 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$), major isomer: δ 7.51 (2H, d, *J*=8.4 Hz, ArH), 7.09 (2H, d, *J*=7.6 Hz, ArH). 6.90–7.00 (4H, m, ArH), 5.47–5.54 (1H, m, NH), 4.41 (1H, dd, *J*=5.2, 7.6 Hz, *CH*NH), 3.38 (1H, dd, *J*=5.2, 11.2 Hz, *CH*OH), 2.36 (3H, s, CH_3), 2.28 (3H, s, CH_3), 1.97–2.0 (1H, br, OH), 1.61–1.69 (1H, m, CH), 0.88–0.93 (6H, m, 2×CH_3). Minor isomer: δ 7.51 (2H, d, *J*=8.4 Hz, ArH), 7.09 (2H, d, *J*=7.6 Hz, ArH). 6.90–7.00 (4H, m, ArH), 5.47–5.54 (1H, m, NH), 4.43 (1H, d, *J*=4.4 Hz, *CH*NH), 3.46–3.51 (1H, m, *CH*OH), 2.36 (3H, s, CH_3), 2.28 (3H, s, CH_3), 2.02–2.04 (1H, br, OH), 1.61–1.69 (1H, m, CH), 0.88–0.93 (6H, m, 2×CH_3). *m/z* (%): 274 ($M^+-17-56$, 32.09), 192 (7.55), 155 (25.01), 121 (10.45), 120 (100). Anal. $C_{19}H_{25}NO_3S$. Calcd C, 65.68; H, 7.25; N, 4.03. Found C, 65.71; H, 7.29; N, 3.96%.

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