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UTILIZATION OF 2-HALO-1,3,4-THIADIAZOLES IN THE SYNTHESIS OF 2-FUNCTIONALIZED 1,3,4-THIADIAZOLE DERIVATIVES

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Abstract – Novel 2-bromo/iodo-5-aryloxymethyl-1,3,4-thiadiazoles were prepared by the diazotization of 2-amino-1,3,4-thiadiazoles using *p*-TsOH as acid under the copper-free conditions. 2-Chloro-5-aryloxymethyl-1,3,4-thiadiazoles, which were prepared by traditional diazotization, were treated with various nucleophiles to give a series of 2-substituted-1,3,4-thiadiazole derivatives including 2-methylamino/ethylamino/hydroxylethylamino/ hydrazinyl-5-aryloxymethyl-1,3,4-thiadizoles and 6-aryloxymethyl[1,2,4]-triazolo[3,4-*b*][1,3,4]thiadiazoles.

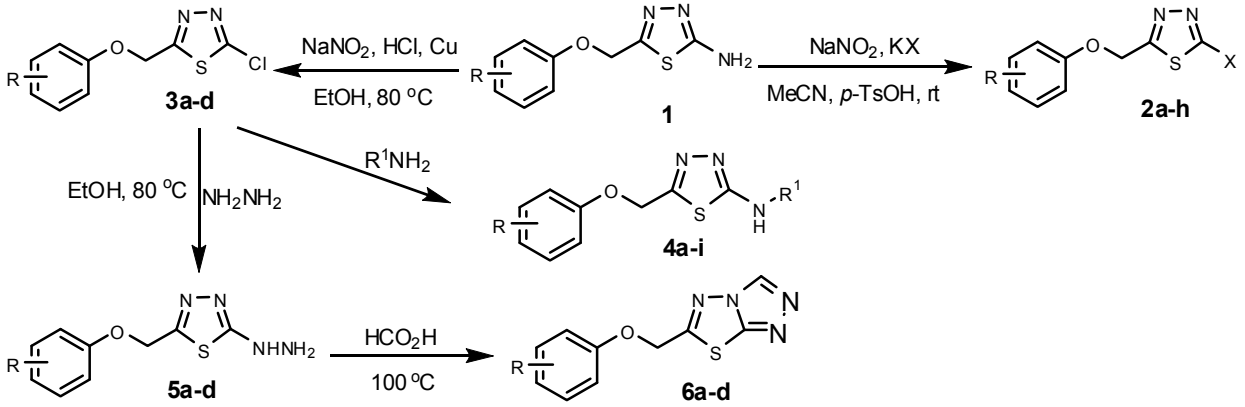
INTRODUCTION

1,3,4-Thiadiazoles are five-membered aromatic heterocycles with great utility in synthetic, medicinal, agricultural, and materials chemistry.[1-4] The widespread use of 1,3,4-thiadiazoles as a scaffold in medicinal chemistry establishes this moiety as an important bio-active class of heterocycles. It has also been reported in literature that 2-methyl/ethylamino-1,3,4-thiadiazole and [1,2,4]triazolo-[3,4-*b*][1,3,4]thiadiazoles exhibit diverse biological properties, including antibacterial,[5] antimicrobial,[6] analgesic,[7] anticancer,[8,9] anti-inflammatory,[10] antidepressant[11] and anti-HIV[12] activities. On the other hand, halides of 1,3,4-thiadiazoles are important building blocks in modern organic synthesis, which

could produce many derivatives from S_N displacement by nucleophiles, such as methylamine, ethylamine, hydroxyethylamine, hydrazine hydrate. Generally, chlorides of 1,3,4-thiadiazoles are obtained by the diazotization of 2-amino-1,3,4-thiadiazoles with sodium nitrite, Cu powder in conc. hydrochloric acid.[13] Recently, progressive one-pot methods for the introduction of iodine into an aromatic substrate have been suggested. These methods use a sequence involving diazotization-iodination of the corresponding amines with HI/KNO_2 in DMSO[14] or KI/$NaNO_2$/*p*-TsOH in CH_3CN.[15] Victor *et al.*[16] have reported the synthesis of stable arenediazonium tosylates by using a polymer-supported diazotization reagent ("Resin–NO_2^-"), then, these salts effectively reacted at room temperature with KI, KBr to give the corresponding halides. Although many important processes in organic chemistry and biochemistry involve C-X (Cl, Br, I) formation by diazotization, the synthesis of 2-bromo/iodo-5-aryloxymethyl-1,3,4-thiadiazoles has not been reported.

A triazolothiadiazole system can be viewed as a cyclic analogue of two very important components-thiosemicarbazide[17,18] and biguanide,[19] which often display diverse biological activities. [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles were prepared by treatment of 4-amino-5-substituted-3-mercapto-1,2,4-triazoles with (un)substituted aromatic acids in the presence of phosphorous oxychloride, usually under harsh conditions.[20] Moreover, condensation of 1,2,4-triazoles with the acids either in PPA or with para-toluenesulfonyl chloride in toluene or under microwave irradiation in DMF.[21,22] Recently, Belen Batanero *et al.* have reported the synthesis of the final products by anodic oxidation in acetonitrile of 2-arylidene-1-(5-aryl-1,3,4-thiadiazol-2-yl)hydrazine.[23]

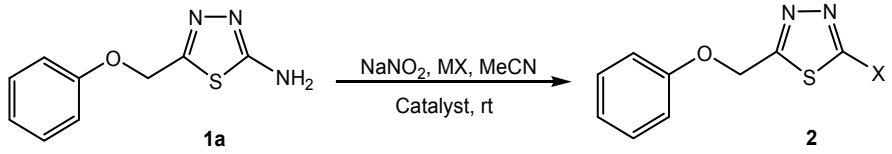
In the previous reports, we demonstrated the use of 2-amino-5-aryl/aryloxymethyl 1,3,4-thiadiazoles as versatile building blocks for the synthesis of functionalized heterocycles, such as 1,3,4-thiadiazole functionalized *N*-phenylacetamide,[24] 5*H*,6*H*-[1,3,4]thiadiazolo[3,2-*a*]pyrimidine-7-one,[25] 2-(5-substituted-1,3,4-thiadiazol-2-ylimino)-4-thiazolidinones,[26] 2-(*N*-formyl)-1,3,4-thiadiazoles.[27] We now report the investigations on the use of 2-amino-5-aryloxymethyl-1,3,4-thiadiazoles **1** for the synthesis of 2-halo-5-aryloxymethyl-1,3,4-thiadiazoles **2-3** and their derivatives, such as, 2-methylamino/ethylamino/hydroxylethylamino-5-aryloxymethyl-1,3,4-thiadizoles **4a-i**, 2-hydrazinyl-5-aryloxymethyl-1,3,4-thiadizoles **5a-d**, and 6-aryloxymethyl[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles **6a-d** (Scheme 1).



Scheme 1

RESULTS AND DISCUSSIONS

Table 1. Optimization of reaction conditions for compound **2a**[a]



Entry	MX	Catalyst	Time (h)	Yield (%)[b]
1	KCl	*p*-TsOH	12	-[c]
2	KCl	PEG-O-SO_3H	12	-
3	KCl	SiO_2-O-SO_3H	12	-
4	NaCl	*p*-TsOH	12	-
5	LiCl	*p*-TsOH	12	-
6	KI	*p*-TsOH	0.5	54
7	KI	*p*-TsOH	1	75
8	KI	*p*-TsOH	2	87
9	KI	PEG-O-SO_3H	2	-
10	KI	SiO_2-O-SO_3H	2	-
11	KBr	*p*-TsOH	2	84

[a] Molar ratio of reagents **1a**/$NaNO_2$/MX/catalyst = 1:2:2.5:3.
[b] Isolated yield.
[c] No detected the product.

We have recently reported the synthesis of 2-chloro-1,3,4-thiadiazoles by diazotization of the 2-amino-1,3,4-thiadiazoles with sodium nitrite, Cu powder in conc. hydrochloric at low temperature.[24] In

order to obtain these compounds under a mild conditions in the absence of copper or HCl, experiments were carried out for the halogenation reaction of 2-amino-1,3,4-thiadiazoles using the reaction for **2a** as a typical reaction (Table 1). Our initial attempts was conducted using *p*-TSA, PEG-O-SO_3H,[28] and SiO_2-O-SO_3H[29] as catalyst and KCl as source of chloride. However, no product **3a** was observed (entries 1-3). Therefore, we screened different salts LiCl, NaCl, KI, and KBr in subsequent experiments (entries 4-11). No chloro-1,3,4-thiadiazole was detected. Interestingly, we found that 2-iodo- and bromo-1,3,4-thiadiazoles can be obtained in good yields. The best yield of **2a** (87%) was obtained by carrying out the reaction at room temperature for 2 h using *p*-toluenesulfonyl acid as catalyst (entry 8). The acid catalyst has a significant effect on the yield of the reaction and no desired 2-iodo-1,3,4-thiasiazole was obtained in the presence of PEG-O-SO_3H, SiO_2-O-SO_3H (entries 9-10).

These optimal reaction conditions were applied to investigate the scope of the reaction. A wide array of 2-amino-1,3,4-thiadiazoles were subjected to the reaction, and corresponding 2-bromo- and iodo-1,3,4-thidadizaoles (**2a-h**) were isolated in good yields (Table 2).

Table 2. Synthesis of 2-bromo- and iodo-1,3,4-thidadizaoles **2a-h**[a]

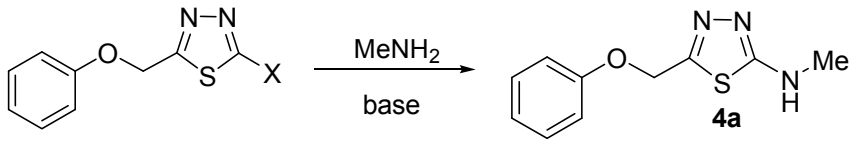
Entry	Product	X	R	Yield (%)[b]
1	**2a**	I	H	87
2	**2b**	I	2-Cl	76
3	**2c**	I	4-Me	91
4	**2d**	I	4-Cl	79
5	**2e**	Br	H	84
6	**2f**	Br	2-Cl	73
7	**2g**	Br	4-Me	89
8	**2h**	Br	4-Cl	75

[a] Reaction conditions: (1) Compound **1** (10 mmol), *p*-TsOH (30 mmol), MeCN (25 mL), rt; (2) $NaNO_2$ (20 mmol), KI/KBr (25 mmol) in H_2O (6 mL), rt, 2 h.
[b] Isolated yield.

Then we investigated nucleophilic substitution of 2-halo-1,3,4-thiadiazoles with several fatty amines (methylamine, ethylamine, hydroxyethylamine) (Table 3). Initially, the reaction mixture of 2-chloro-thiadiazole **3a,** methylamine and K_2CO_3 was reacted for 8 h in ethanol at room temperature and the

corresponding compound **4a** was obtained with low yield (42%). The employment of 2-bromo- and 2-iodo-thiadiazole (**2a** and **2e**) in the same reaction conditions also gave the product **4a**, however, with more lower yield (36% and 10%) (entries 1-3). When **3a** reacted with methylamine in the presence of NaOH, the yield of **4a** was 35%. Consequently, other temperature was tested and the best yield of **4a** (86%) was obtained by carrying out the reaction in the absence of a base at 80 °C for 3 h (entries 5-7). Subsequently, 2-bromo- and 2-iodo-thiadiazole (**2a** and **2e**) were examined in the same reaction condition and the yields of **4a** were 67% and 49% (entries 8 and 9). Therefore, 2-chloro-1,3,4-thiadiazole **3a** as the starting material was treated with ethylamine and hydroxyethylamine to allow the reactions to proceed smoothly and afforded the desired products **4b, c** in high yields. In comparison with the yields of **4a-c,** we found out that the nucleophilic activity of fatty amines probably was CH_3NH_2 > $CH_3CH_2NH_2$ > $HOCH_2CH_2NH_2$. Then, other 2-chloro-1,3,4-thiadiazoles with electron-withdrawing groups as well as electron-donating groups, were transformed into corresponding compounds **4d-i** in good yields (Table 4).

Table 3. The synthesis of compound **4a** under various conditions[a]



Entry	X	Base	Temp. (°C)	Time (h)	Yield (%)[b]
1	Cl	K_2CO_3	25	8h	42
2	Br	K_2CO_3	25	8h	36
3	I	K_2CO_3	25	8h	10
4	Cl	NaOH	25	8h	35
5	Cl	-	40	8h	51
6	Cl	-	60	8h	64
7	Cl	-	80	3h	86
8	Br	-	80	3h	67
9	I	-	80	3h	49

[a] Conditions: halides (1 mmol), methylamine (3 mmol), base (2 mmol), EtOH (10 mL).
[b] Isolated yield.

Table 4. Synthesis of 2-alkylamino-1,3,4-thiadiazoles **4a-i**[a]

Entry	Product	R	R^1	Yield (%)[b]
1	**4a**	H	Me	86
2	**4b**	H	Et	82
3	**4c**	H	CH_2CH_2OH	80
4	**4d**	4-Me	Me	84
5	**4e**	4-Me	Et	75
6	**4f**	4-Me	CH_2CH_2OH	69
7	**4g**	2-Cl	Me	87
8	**4h**	2-Cl	Et	83
9	**4i**	2-Cl	CH_2CH_2OH	76

[a] Reaction conditions: Fatty amine (3 mmol), compound **3** (1 mmol), EtOH (10 mL), 80 °C, 3h.
[b] Isolated yield.

The reaction for 2-alkylamino-1,3,4-thiadiazoles led us to investigate the synthesis of 2-hydrazino-1,3,4-thiadiazole and its cyclization reaction. When 2-chloro-1,3,4-thiadiazoles **3** and hydrazine hydrate were stirred in ethanol under reflux, the corresponding **5a-d** were obtained in good yields after 3 h. Subsequently, compound **5** was treated with formic acid leading to the 6-aryloxymethyl[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles **6a-d** (Table 5).

In conclusion, 2-bromo/iodo-5-aryloxymethyl-1,3,4-thiadiazoles, 2-methylamino/ethylamino/ hydroxylmethyl/hydrazinyl-5-aryloxymethyl-1,3,4-thiadiazole and 6-aryloxymethyl[1,2,4]triazolo-[3,4-*b*][1,3,4]thiadiazoles using readily available 2-amino-5-aryloxymethyl-1,3,4-thiadiazoles as starting material were prepared. To the best of our knowledge, these compounds have not been reported previously. Furthermore, synthesis and screening of desired compounds based on 1,3,4-thiadiazole scaffolds may lead to the discovery of interesting biological activities.

Table 5. Synthesis of 2-hydrazinyl-1,3,4-thiadiazole 5a-d and [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles **6a-d**[a]

Entry	Product	R	Isolated Yield(%)
1	**5a**	H	79
2	**5b**	4-Me	89
3	**5c**	2-Cl	73
4	**5d**	4-OMe	83
5	**6a**	H	80
6	**6b**	4-Me	84
7	**6c**	2-Cl	78
8	**6d**	4-OMe	82

[a] Reaction conditions: **5a-d**: compound **3** (2 mmol) in EtOH (20 mL), hydrazine hydrate (3 mmol), 80 °C, 3h; **6a-d**: compound **5** (1 mmol), HCO_2H (5 mL), 100 °C, 2h.
[b] Isolated yield.

EXPERIMENTAL

All reagents were obtained commercially and used without further purification. Melting points were determined on an XT-4 electrothermal micromelting point apparatus and uncorrected. IR spectra were recorded using KBr pellets on Nicolet AVATAR 36 FT-IR spectrophotometer. NMR spectra were recorded at 400 (^{1}H) and 100 (^{13}C) MHz, respectively, on a Varian Mercury plus-400 instrument using $CDCl_3$ or DMSO-d_6 as solvent and TMS as internal standard. Elemental analyses were performed on a Carlo-Erba 1106 Elemental Analysis instrument. 2-Amino-5-aryloxymethyl-1,3,4-thiadiazoles[30] and 2-chloro-5-aryloxymethyl-1,3,4-thiadiazoles[24] were prepared as described in the literature procedures.

General procedure for compounds 2a-h. To a solution of *p*-TsOH (30 mmol) in MeCN (25 mL) was added the 2-amino-1,3,4-thiadiazoles (10 mmol) at rt. The resulting suspension of amine salt was added gradually a solution of $NaNO_2$ (20 mmol) and KI/KBr (25 mmol) in H_2O (6 mL). This process was completed for 30 min. Then the reaction mixture was stirred at rt for 2 h. To the reaction mixture was then added H_2O (100 mL), 1 M $NaHCO_3$ aqueous (until pH = 9-10) and $Na_2S_2O_3$ (2 M, 30 mL). The precipitated aromatic iodide was filtered or extracted with EtOAc and purified by flash chromatography

(petroleum-EtOAc, 1: 6)

2a: Yield 87%; mp 99-100 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.36-7.00 (m, 5H, H_{Ar}), 5.64 (s, 2H, OCH_2). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 172.2, 157.2, 129.8 (2C), 122.0, 115.4 (2C), 112.2, 63.6. IR (KBr) *v*: 3443, 1597, 1496, 1245 cm^{-1}. MS: *m/z* = 318 (M^+). Anal. Calcd for $C_9H_7IN_2OS$ (317.93): C 33.98, H 2.22, N 8.81. Found: C 34.12, H 2.28, N 8.73.

2b: Yield 76%; mp 133-135 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.02-6.93(m, 4H, H_{Ar}), 5.52 (s, 2H, OCH_2). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 178.5, 158.2, 155.4, 129.6, 127.8, 122.9，122.3，116.6, 65.0. IR (KBr) *v*: 3324, 3179, 1577, 1228 cm^{-1}. MS: *m/z* = 352 (M^+). Anal. Calcd for $C_9H_6ICIN_2OS$ (351.89): C 30.66, H 1.72, N, 7.95. Found: C 30.52, H 1.79, N 7.87.

2c: Yield 91%; mp 159-161 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.26-6.83 (m, 4H, H_{Ar}), 5.58 (s, 2H, OCH_2), 2.37 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 171.5, 157.0, 158.4, 127.6 (2C), 124.5, 120.8, 114.2, 65.0, 15.8. IR (KBr) *v*: 3327, 3169, 1591, 1221 cm^{-1}. MS: *m/z* = 332 (M^+). Anal. Calcd for $C_{10}H_9IN_2OS$ (331.95): C 36.16, H 2.73, N 8.43. Found: C 36.31, H 2.62, N 8.58.

2d: Yield 79%; mp 184-186 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.02-7.11 (m, 4H, H_{Ar}), 5.54 (s, 2H, OCH_2). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 175.5, 156.2, 131.6, 129.8 (2C), 121.9, 117.6 (2C), 65.0. IR (KBr) *v*: 3319, 3174, 1587, 1231 cm^{-1}. MS: *m/z* = 352 (M^+), 354 (M+2). Anal. Calcd for $C_9H_6ICIN_2OS$ (351.89): C 30.66, H 1.72, N 7.95. Found: C 30.54, H 1.67, N 8.01.

2e: Yield 84%; mp 48-50 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34-6.96 (m, 5H, H_{Ar}), 5.46 (s, 2H, OCH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.4, 157.1, 140.1, 129.8 (2C), 122.3, 114.7 (2C), 64.7. IR (KBr) *v*: 3441, 3062, 1595, 1492, 1244 cm^{-1}. MS: *m/z* = 270 (M^+), 272 (M+2). Anal. Calcd for $C_9H_7BrN_2OS$ (269.95): C, 39.87; H, 2.60; N, 10.33. Found: C 39.98, H 2.54, N 10.42.

2f: Yield 73%; mp 109-111 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43-6.99 (m, 4H, H_{Ar}), 5.52 (s, 2H, OCH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.8, 152.8, 140.5, 130.7, 128.0, 123.5, 123.3, 114.3, 66.0. IR (KBr) *v*: 3456, 2924, 1585, 1478, 1290 cm^{-1}. MS: *m/z* = 304 (M^+) 306 (M+2). Anal. Calcd for $C_9H_6BrClN_2OS$ (303.91): C 35.37, H 1.98, N 9.17. Found: C 35.45, H 1.91, N 9.26.

2g: Yield 89%; mp 99-101 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26-6.86 (m, 4H, H_{Ar}), 5.43 (s, 2H, OCH_2). 2.30 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.7, 155.0, 140.1, 131.8 (2C), 130.2, 114.6 (2C), 65.0, 20.5. IR (KBr) *v*: 3447, 2918, 1609, 1508, 1242 cm^{-1}. MS: *m/z* = 284 (M^+) 286 (M+2). Anal. Calcd for $C_{10}H_9BrN_2OS$ (283.96): C 42.12, H 3.18, N 9.82. Found: C 42.23, H 3.14, N 9.95.

2h: Yield 75%; mp 85-87 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.56-6.83 (m, 4H, H_{Ar}), 5.36 (s, 2H, OCH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.6, 151.3, 139.7, 128.3 (2C), 121.8, 112.6 (2C), 64.8. IR (KBr) *v*: 3448; 2917; 1576; 1407; 1273 cm^{-1}. MS: *m/z* = 304 (M^+) 306 (M+2). Anal. Calcd for $C_9H_6BrClN_2OS$ (303.91): C 35.37, H 1.98, N 9.17. Found: C 35.12, H 1.92, N 9.28.

General procedure for the synthesis of compounds 4a-i. Fatty amine (3 mmol) was added to a solution of compound **3** (1 mmol) in EtOH (10 mL). Then the reaction mixture was refluxed for 3 h and quenched to ice water. Then the precipitate was filtered off and crystallized from acetone with petroleum ether to afford compounds **4**.

4a: Yield 86%; mp 88-90 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32-6.98 (m, 5H, H_{Ar}), 6.34 (s, 1H, NH), 5.28 (s, 2H, OCH_2), 3.04 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.8, 157.6, 155.4, 129.6 (2C), 121.8, 114.8 (2C), 64.9, 33.3. IR (KBr) *v*: 3222, 2942, 1586 cm^{-1}. MS: *m/z* = 221 (M^+). Anal. Calcd for $C_{10}H_{11}N_3OS$ (221.06): C 54.28, H 5.01, N 18.99. Found: C 54.06, H 5.04, N 18.92.

4b: Yield 82%; mp 98-100 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32-6.97 (m, 5H, H_{Ar}), 5.84 (s, 1H, NH), 5.28 (s, 2H, OCH_2), 3.34 (q, *J* = 8.0 Hz, 2H, CH_2CH_3), 1.31 (t, *J* = 8.0 Hz, 3H, CH_2CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.3, 157.5, 155.1, 129.6 (2C), 121.6, 114.9 (2C), 64.8, 42.0, 14.6. IR (KBr) *v*: 3187, 2924, 1581 cm^{-1}. MS: *m/z* = 235 (M^+). Anal. Calcd for $C_{11}H_{13}N_3OS$ (235.08): C 56.15, H 5.57, N 17.86. Found: C 56.39, H 5.54, N 17.80.

4c: Yield 80%; mp 62-64 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31-6.97 (m, 5H, H_{Ar}), 6.87 (s, 1H, NH), 5.29 (s, 2H, OCH_2), 3.91 (t, *J* = 4.0 Hz, 2H, CH_2OH), 3.53 (t, *J* = 4.0 Hz, 2H, CH_2CH_2), 2.79 (s, 1H, OH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.3, 157.5, 155.7, 129.5 (2C), 121.7, 114.8 (2C), 64.8, 61.2, 49.2. IR (KBr) *v*: 3270, 2918, 1511 cm^{-1}. MS: *m/z* = 251 (M^+). Anal. Calcd for $C_{11}H_{13}N_3O_2S$ (251.07): C 52.57 H 5.21, N 16.72. Found: C 52.34, H 5.24, N 16.78.

4d: Yield 84%; mp 113-115 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.09 (d, *J* = 8.0 Hz, 2H, H_{Ar}), 6.89 (d, *J* = 8.0 Hz, 2H, H_{Ar}), 6.34 (s, 1H, NH), 5.27 (s, 2H, OCH_2), 3.03 (s, 2H, CH_3), 2.23 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.6, 155.5, 155.3, 130.4 (2C), 130.1, 115.0 (2C), 64.5, 33.3, 20.3. IR (KBr) *v*: 3206, 2917, 1585 cm^{-1}. MS: *m/z* = 235 (M^+). Anal. Calcd for $C_{11}H_{13}N_3OS$ (235.08): C 56.15, H 5.57, N 17.86. Found: C 55.84, H 5.61, N 17.75.

4e: Yield 75%; mp 128-130 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.08 (d, *J* = 8.0 Hz, 2H, H_{Ar}), 6.89 (d, *J*

= 8.0 Hz, 2H, H_{Ar}), 5.85 (s, 1H, NH), 5.27 (s, 2H, OCH_2), 3.35 (q, *J* = 8.0 Hz, 2H, C*H*$_2$CH$_3$), 2.23 (s, 3H, CH_3), 1.32 (t, *J* = 8.0 Hz, 3H, CH_2CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.2, 155.70, 154.9, 130.3 (2C), 130.2, 115.1 (2C), 64.3, 42.1, 20.5, 14.6. IR (KBr) *v*: 3168, 2924, 1581 cm^{-1}. MS: *m/z* = 249 (M^+). Anal. Calcd for $C_{12}H_{15}N_3OS$ (249.09): C 57.81, H 6.06, N 16.85. Found: C 58.01, H 6.03, N 16.94.

4f: Yield 69%; mp 74-76 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.09 (d, *J* = 8.0 Hz, 2H, H_{Ar}), 6.90 (d, *J* = 8.0 Hz, 2H, H_{Ar}), 6.88 (s, 1H, NH), 5.26 (s, 2H, OCH_2), 3.90 (t, *J* = 4.0 Hz, 2H, C*H*$_2$OH), 3.51 (t, *J* = 4.0 Hz, 2H, C*H*$_2$CH$_2$), 2.78 (s, 1H, OH), 2.24 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.2, 155.8, 155.3, 130.2 (2C), 130.1, 115.1 (2C), 64.9, 42.1, 20.5, 14.6. IR (KBr) *v*: 3277, 2918, 1511 cm^{-1}. MS: *m/z* = 265 (M^+). Anal. Calcd for $C_{12}H_{15}N_3O_2S$ (265.09): C 54.32, H 5.70, N 15.84. Found: C 54.55, H 5.66, N 15.93.

4g: Yield 87%; mp 118-120 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40-6.97 (m, 4H, H_{Ar}), 6.35 (s, 1H, NH), 5.34 (s, 2H, OCH_2), 3.03 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.7, 155.4, 153.0, 130.5, 128.0, 123.2, 122.6, 114.5, 65.9, 33.3. IR (KBr) *v*: 3130, 2949, 1549 cm^{-1}. MS: *m/z* = 255 (M^+). Anal. Calcd for $C_{10}H_{10}ClN_3OS$ (255.02): C 46.97, H 3.94, N 16.43. Found: C 47.22, H 3.96, N 16.35.

4h: Yield 83%; mp 103-105 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40-6.95 (m, 4H, H_{Ar}), 5.85 (s, 1H, NH), 5.35 (s, 2H, OCH_2), 3.35 (q, *J* = 8.0 Hz, 2H, C*H*$_2$CH$_3$), 1.32 (t, *J* = 8.0 Hz, 3H, CH_2CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.3, 155.1, 153.0, 130.6, 128.0, 123.4, 122.7, 114.5, 66.0, 42.1, 14.7. IR (KBr) *v*: 3193, 2919, 1581 cm^{-1}. MS: *m/z* = 269 (M^+) 271 (M+2). Anal. Calcd for $C_{11}H_{12}ClN_3OS$ (269.04): C 48.98, H 4.48, N 15.58. Found: C 49.23, H 4.46, N 15.51.

4i: Yield 76%; mp 138-139 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39-6.94 (m, 4H, H_{Ar}), 6.87 (s, 1H, NH), 5.34 (s, 2H, OCH_2), 3.90 (t, *J* = 4.0 Hz, 2H, C*H*$_2$OH), 3.52 (t, *J* = 4.0 Hz, 2H, C*H*$_2$CH$_2$), 2.78 (s, 1H, OH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.2, 155.7, 153.1, 130.5, 127.8, 123.5, 122.8, 114.3, 65.8, 61.1. IR (KBr) *v*: 3187, 2904, 1572 cm^{-1}. MS: *m/z* = 285 (M^+) 287 (M+2). Anal.calcd for $C_{11}H_{12}ClN_3O_2S$ (285.03): C 46.24, H 4.23, N 14.71. Found: C 46.02, H, 4.25, N 14.65.

General procedure for the preparation of compounds 5a-d. To the solution of compound **3** (2 mmol) in EtOH (20 mL) was added hydrazine hydrate solution (85%) in water (3 mmol) and refluxed for 3 h. After completion of the reaction, the reaction mixture was concentrated and cooled to rt to give a solid. Then the precipitation was filtered and recrystallized from EtOH and DMF to give the product **5**.

5a: Yield 79%; mp 154-156 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.80 (s, 1H, NH), 7.30-6.95 (m, 5H, H_{Ar}), 5.28 (s, 2H, OCH_2), 5.11 (s, 2H, NH_2). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 178.5, 157.5, 155.4, 129.6 (2C), 121.8, 114.9 (2C), 65.0. IR (KBr) v: 3324, 3179, 2929, 1594 cm^{-1}. MS: m/z = 222 (M^+). Anal. Calcd for $C_9H_{10}N_4OS$ (222.06): C 48.63, H 4.53, N 25.21. Found: C 48.88, H 4.51, N 25.36.

5b: Yield 89%; mp 187-189 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.82 (s, 1H, NH), 7.10 (d, J = 8.0 Hz, 2H, H_{Ar}), 6.92 (d, J = 8.0 Hz, 2H, H_{Ar}), 5.24 (s, 2H, OCH_2), 5.10 (s, 2H, NH_2), 2.24 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 178.4, 155.4, 154.9, 130.3 (2C), 130.0, 115.0 (2C), 64.5, 20.2. IR (KBr) v: 3323, 3192, 2927, 1563 cm^{-1}. MS: m/z = 236 (M^+). Anal. Calcd for $C_{10}H_{12}N_4OS$ (236.07): C 50.83, H 5.12, N 23.71. Found: C 51.11, H 5.09, N 23.85.

5c: Yield 73%; mp 176-178 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.82 (s, 1H, NH), 7.39-6.95 (m, 4H, H_{Ar}), 5.35 (s, 2H, OCH_2), 5.10 (s, 2H, NH_2).^{13}C NMR (100 MHz, DMSO-d_6): δ = 178.3, 154.8, 153.1, 130.5, 127.9, 123.3, 122.7, 114.4, 65.9. IR (KBr) v: 3314, 3161, 2924, 1587 cm^{-1}. MS: m/z = 256 (M^+) 258 (M+2). Anal. Calcd for $C_9H_9ClN_4OS$ (256.02): C 42.11, H 3.53, N 21.82. Found: C 41.90, H 3.52, N 21.90.

5d: Yield 83%; mp 147-149 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.82 (s, 1H, NH), 7.07-6.68 (m, 4H, H_{Ar}), 5.37 (s, 2H, OCH_2), 5.31 (s, 2H, NH_2), 3.78 (s, 3H, OCH_3).^{13}C NMR (100 MHz, DMSO-d_6): δ = 179.1, 159.5, 150.9 (2C), 126.3 (2C), 116.7 (2C), 66.8, 57.6. IR (KBr) v: 3345, 3172, 2926, 1557 cm^{-1}. MS: m/z = 252 (M^+). Anal. Calcd for $C_{10}H_{12}N_4O_2S$ (252.07): C 47.61, H 4.79, N 22.21. Found: C 47.76, H 4.72, N 22.19.

General procedure for compounds 6a–d. The solution of compound **5** (1 mmol) in formic acid (5 mL) was refluxed for 2 h. After completion of the reaction, the excess formic acid was evaperated under reduce pressure. Then the residue was quenched to ice water and neutralized with saturated $NaHCO_3$ aqueous. The precipitation was filtered and the crude product was recrystallized from EtOH to give pure compounds **6a-d**.

6a: Yield 80%; mp 136-138 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.60 (s, 1H, CH), 7.39-7.35 (m, 2H, H_{Ar}), 7.13-7.03 (m, 3H, H_{Ar}), 5.70 (s, 2H, OCH_2). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 167.8, 157.1, 136.4, 129.9, 122.2, 115.1, 64.7. IR (KBr) v: 3341, 3111, 2923, 1593 cm^{-1}. MS: m/z = 232 (M^+). Anal. Calcd for $C_{10}H_8N_4OS$ (232.04): C 51.71, H 3.47, N 24.12. Found: C 51.60, H 3.56, N 24.01.

6b: Yield 84%; mp 134-136 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.49 (s, 1H, CH), 7.15 (d, J = 8.0 Hz, 2H, H_{Ar}), 6.92 (d, J = 8.0 Hz, 2H, H_{Ar}), 5.52 (s, 2H, OCH_2), 2.42 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 167.5, 157.1, 152. 6, 138.2, 126.0, 122.2, 115.3, 65.7, 19.6. IR (KBr) v: 3329, 3106, 2920, 1585cm^{-1}. MS: m/z = 246 (M^+). Anal. Calcd for $C_{11}H_{10}N_4OS$ (246.06): C53.64, H 4.09, N 22.75. Found: C 53.55, H 4.17, N 22.86.

6c: Yield 78%; mp 130-132 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.55 (s, 1H, CH), 7.19-6.88 (m, 4H, H_{Ar}), 5.41 (s, 2H, OCH_2), 3.77 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 167.2, 156.1, 152.4, 141.8, 136.0, 122.2, 115.1, 64.7. 55.6. IR (KBr) v: 3339, 3109, 2920, 1590 cm^{-1}. MS: m/z = 266 (M^+) 268 (M+2). Anal. Calcd for $C_{10}H_7ClN_4OS$ (266.00): C 45.03, H 2.65, N 21.01. Found: C 45.11, H 2.68, N 21.13.

6d: Yield 82%; mp 135-137 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.51 (s, 1H, CH), 7.01-6.83 (m, 4H, H_{Ar}), 5.43 (s, 2H, OCH_2), 3.78 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 167.2 161.1, 152.4, 151.4, 139.8, 136.4, 122.7, 115.1, 64.5, 55.9. IR (KBr) v: 3340, 3110, 2922, 1591cm^{-1}. MS: m/z = 262 (M^+). Anal. Calcd for $C_{11}H_{10}N_4O_2S$ (262.05): C 50.37, H 3.84, N 21.36. Found: C 50.15, H 3.80, N 21.47.

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