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Oxidation of 3,4-dihydropyrimidin-2(1*H*)-thione using (diacetoxyiodo) benzene: unprecedented formation of substituted 2-(1,4-dihydropyrimidin-2-ylthio)pyrimidine

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ABSTRACT

4-Aryl-6-methyl-3,4-dihydropyrimidin-2(1*H*)-thione scaffolds of Biginelli type were oxidized using (diacetoxyiodo)benzene and the reaction afforded 2-(1,4-dihydropyrimidin-2-ylthio)pyrimidine derivatives through an unprecedented oxidation–desulfurization process.

Recent decades have witnessed an exponential growth in the applications of hypervalent iodine reagents for carrying out a number of oxidative transformations.[1] These reagents are commercially available, mild, highly selective and resemble in reactivity with heavy metal reagents without the toxicity and environmental issues.[2] Currently, both iodine(III) and iodine(V) reagents are widely used in organic synthesis.[3] (Diacetoxyiodo)benzene (DIB) is one of the most extensively used parent hypervalent iodine(III) reagent and its reactions with various nitrogen, sulfur and oxygen nucleophilic compounds are known.[4] In particular, the reactions of DIB with nucleophilic sulfur compounds such as thiols,[5] thioamides,[6] thioureas,[7] sulfides,[8] and ammonium thiocyanate[9] have resulted in useful functional group interconversions as well as in the formation of heterocycles.

Recently, it has been revealed by Singh et al. that the acyclic 1,3-disubstituted thiourea undergoes desulfurization reaction with DIB leading to the formation of N-acylated ureas via carbodiimide intermediate.[7a] The 3,4-dihydropyrimidin-2(1*H*)-thione, which can be easily obtained by Biginelli reaction,[10] is a structural analog of cyclic thiourea and therefore, we were interested to find out the fate of this compound in the oxidation reaction using hypervalent iodine reagents. Owing to the simplicity of an original three-component Biginelli reaction, the direct oxidative dehydrogenation of 3,4-dihydropyrimidin-2(1*H*)-one or 3,4-dihydropyrimidin-2(1*H*)-thione has been long desired for the formation of aromatized pyrimidine which is a common structural motif found in many biologically active compounds.[11] However, there are a few literature reports mainly constrained to the oxidative aromatization of 3,4-dihydropyrimidin-2(1*H*)-one to form pyrimidine under different reaction conditions.[12] In contrast to 3,4-dihydropyrimidin-2(1*H*)-one, there is a great synthetic challenge for oxidative dehydrogenation of 3,4-dihydropyrimidine-2(1*H*)-thione to form pyrimidine because the sulfur functional unit is susceptible for oxidative dimerization and may act as a poison for metal-based catalysts.[13] The reaction of 3,4-dihydropyrimidine-2(1*H*)-thione with alkyl halide followed by oxidative aromatization is one of the most common two-step strategy for the synthesis of highly substituted pyrimidine derivatives (Scheme 1).[14] In another literature report, an attempt has been made to oxidize 3,4-dihydropyrimidine-2(1*H*)-thione using oxone on wet alumina or hydrogen peroxide in the presence of catalytic amount of vanadyl sulfate to provide desulfurated 1,4-dihydropyrimidine, which was further oxidized to 2-unsubstituted pyrimidines by treatment with excess $KMnO_4$.[15] Recently, a successful oxidative transformation of 3,4-dihydropyrimidine-2(1*H*)-thione to symmetrical bis(2-pyrimidyl) disulfides have been achieved by using 100 wt % of activated carbon.[16] Thus, there are very few reports available on the oxidation reactions of 3,4-dihydropyrimidine-2(1*H*)-thione. Herein, we wish to investigate the oxidation reactions of 3,4-dihydropyrimidine-2(1*H*)-thione using hypervalent iodine(III) reagent. We envisaged that the strong electrophilic nature of the hypervalent iodine in combination with the super leaving group ability of

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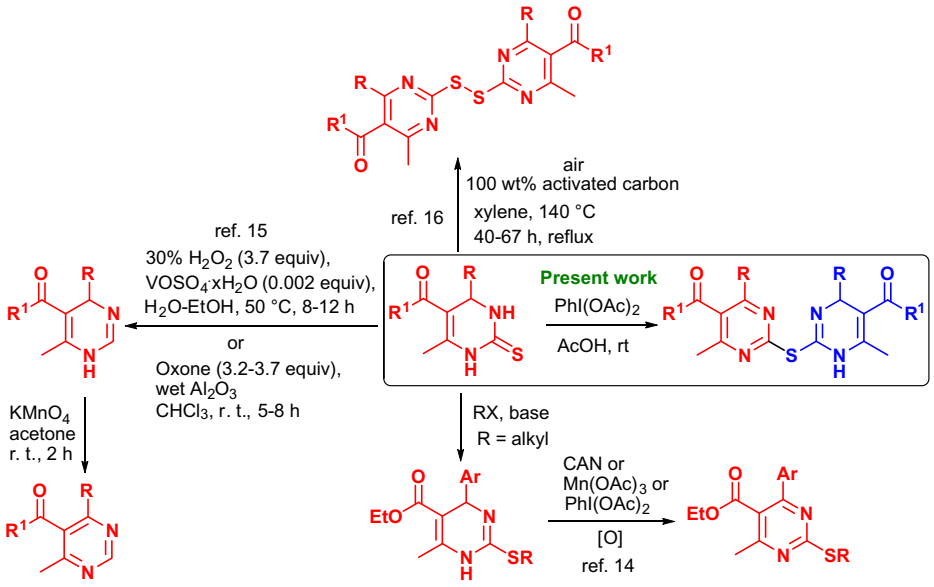
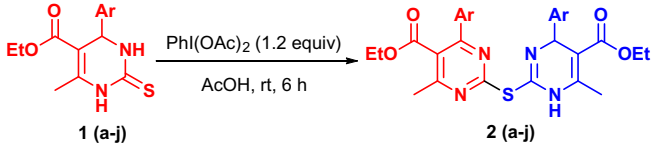


Scheme 1. Literature methods for the oxidation reactions of 3,4-dihydropyrimidine-2(1*H*)-thione.

phenyliodonium group can induce either oxidative dehydrogenation or the oxidative dimerization of 3,4-dihydropyrimidine-2(1*H*)-thione. However, the reaction of DIB with 3,4-dihydropyrimidine-2(1*H*)-thione resulted in the unusual formation of substituted 2-(1,4-dihydropyrimidin-2-ylthio)pyrimidine through oxidation–desulfurization process (Scheme 1). The product of these reactions are derivatives of 2-(1,4-dihydropyrimidin-2-ylthio)pyrimidine which can be regarded as the highly decorated 1,4-dihydropyrimidine type scaffolds at 2-position. It is important to note that these 1,4-dihydropyrimidine and Hantzsch's 1,4-dihydropyridine are considered as the potent mimics of calcium channel modulators of the nifedipine type drugs with a similar pharmacological profile.[17]

The 4-phenyl-6-methyl-3,4-dihydropyrimidine-2(1*H*)-thione **1a** (Table 1) was chosen as a model substrate for the oxidation reaction using (diacetoxyiodo)benzene as the oxidant. The reaction of **1a** with DIB (1.2 equiv) in various solvents such as methanol, acetone, acetonitrile, and dichloromethane was carried out. The progress of the reactions, as monitored by the TLC, indicated that the reaction did not proceed in these solvents and the starting material was found to be almost unreacted. This may be partly attributed to the insolubility of **1a** in methanol, acetone, acetonitrile, and dichloromethane. The complete solubility of **1a** in acetic acid encouraged us to carry out its reaction with DIB (1.2 equiv) and indeed, the formation of unusual product **2a** through oxidation–desulfuration process was observed in 84% yield in 6 h.[18] The ^{1}H NMR analysis of **2a** indicated the presence of two distinct ethyl ester groups giving triplets and quartets at δ 3.99, 4.06, and 1.08, 1.15 ppm, respectively which is reminiscent of unsymmetrical structure of the product **2a**.[19] Further, two singlets were observed at δ 5.34 and 6.20 due to the presence of C-4 and NH protons. The LCMS of **2a** corresponds to the $m/z = 517$ $(M+H)^+$ which clearly confirms the unexpected removal of one sulfur atom.

Table 1
Oxidation of 3,4-dihydropyrimidine-2(1*H*)-thione with (diacetoxyiodo)benzene



1 (a-j) **2 (a-j)**

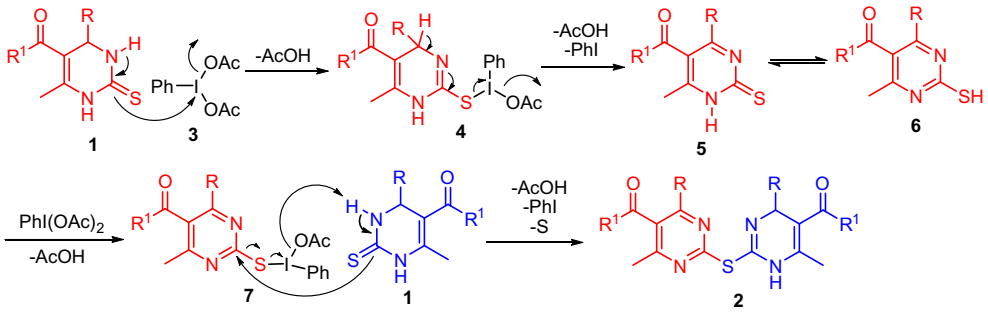
Entry	Substrate **1**	Ar	Product **2**	Yield[a] (%)
a	**1a**	C_6H_5	**2a**	86
b	**1b**	4-MeC_6H_4	**2b**	83
c	**1c**	2-MeOC_6H_4	**2c**	65
d	**1d**	3-MeOC_6H_4	**2d**	74
e	**1e**	4-MeOC_6H_4	**2e**	76
f	**1f**	3,4-$(MeO)_2C_6H_3$	**2f**	73
h	**1g**	2-ClC_6H_4	**2g**	77
i	**1h**	4-ClC_6H_4	**2h**	82
k	**1i**	3-BrC_6H_4	**2i**	71
l	**1j**	4-BrC_6H_4	**2j**	79

[a] Isolated yields after silica gel column chromatography.

The plausible mechanism for the formation of unusual oxidation–desulfurization product **2** is shown in Scheme 2. DIB **3** may undergo ligand association–dissociation process with nucleophilic sulfur of 3,4-dihydropyrimidine-2(1*H*)-thione **1** to form **4**. The tendency of hypervalent iodine for reductive elimination of iodobenzene from **4** results in the formation of **5** which tautomerizes to form **6**. Again, the reaction of DIB **3** with **6** leads to form the key intermediate **7**. The susceptibility of pyrimidine **7** for nucleophilic substitution at 2-position in combination with its tendency for facile reductive elimination of iodobenzene may promote the removal of elemental sulfur with the concomitant nucleophilic attack of another molecule of **1** to form **2**. There is a literature reference for the removal of sulfur from acyclic thiourea type substrate to form either a carbodiimide or guanidine derivatives.[7]

The generality and scope of this oxidation–desulfurization process was investigated by using diverse 4-aryl substituted 3,4-dihydropyrimidine-2(1*H*)-thiones. As shown in Table 1, the presence of electron-donating and withdrawing substituents at C-4 aryl group of 3,4-dihydropyrimidin-2(1*H*)-thiones has little influence on the yields of oxidation–desulfurization products. In all the cases, good to excellent yields of the products were observed.

In conclusion, we have investigated the transition metal-free oxidation reaction of 4-aryl-6-methyl-3,4-dihydropyrimidin-2(1*H*)-thione scaffolds of Biginelli type using (diacetoxyiodo) benzene under mild conditions to form structurally diverse 2-(1,4-dihydropyrimidin-2-ylthio)pyrimidine derivatives. The product of this reaction is unusual due to the removal of one sulfur



Scheme 2. Plausible mechanism for oxidation–desulfurization process.

atom in the oxidative dimerization process of 3,4-dihydropyrimidine-2(1*H*)-thione.

Acknowledgments

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Supplementary data

Supplementary data (copies of NMR (^{1}H and ^{13}C) NMR spectra and LCMS are provided for all the compounds synthesized) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.01.099.

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18. *Representative procedure for the preparation of 2-(1,4-dihydropyrimidin-2-ylthio)pyrimidine derivatives*: DIB (0.386 g, 1.2 mmol) was added to a solution of **1a** (0.276 g, 1 mmol) in acetic acid (10 mL) and the reaction mixture was stirred at rt for 6 h. The progress of the reaction was monitored by TLC. After completion of reaction, water (10 mL) was added and the mixture was extracted with ethyl acetate (3 × 10 mL). Organic layers were combined, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel using petroleum ether/EtOAc 9:1 as eluent to give the desired product **2a** (0.887 g, 86%) as yellow solid in excellent purity.
19. *Characterization data new compounds:*
Compound ***2a***: Yellow solid, mp 162–163 °C. ^{1}H NMR 400 MHz ($CDCl_3$): δ 1.08 (3H, t, J = 7.1 Hz, CH_3), 1.15 (3H, t, J = 7.1 Hz, CH_3), 2.39 (3H, s, CH_3), 2.42 (3H, s, CH_3), 3.99 (2H, q, J = 7.1 Hz, CH_2), 4.06 (2H, q, J = 7.1 Hz, CH_2), 5.46 (1H, s, CH), 6.20 (1H, s, NH), 7.29–7.33 (8H, m, ArH), 7.45–7.48 (2H, m, ArH). ^{13}C NMR 100 MHz ($CDCl_3$): δ 14.07, 14.09, 22.85, 23.25, 56.11, 59.68, 60.30, 102.71, 106.43, 127.10, 127.43, 128.09, 128.28, 128.44, 128.67, 128.92, 129.15, 139.61, 140.06, 148, 97, 153.37, 156.32, 158.52, 165.49, 165.79. IR (cm^{-1}): 2976, 1707, 1606, 1504, 1230, 810, 686. MS (ESI) m/z $(M+H)^+$ Calculated for $C_{28}H_{28}N_4O_4S$: 516.18. Found: 517.10.
Compound ***2b***: Yellow solid, mp 130–132 °C. ^{1}H NMR 400 MHz ($CDCl_3$): δ 1.14 (3H, t, J = 7.1 Hz, CH_3), 1.22 (3H, t, J = 7.1 Hz, CH_3), 2.25 (3H, s, CH_3), 2.38 (6H, s, CH_3), 2.42 (3H, s, CH_3), 4.03 (2H, q, J = 7.1 Hz, CH_2), 4.12 (2H, q, J = 7.1 Hz, CH_2), 5.34(1H, s, CH), 6.20(1H, s, NH), 6.68 (2H, d, J = 8.1 Hz, ArH), 6.82 (2H, d, J = 7.8 Hz, ArH), 7.12 (2H, d, J = 7.9 Hz, ArH), 7.30 (2H, d, J = 8.1 Hz, ArH). ^{13}C NMR 100 MHz ($CDCl_3$): δ 14.16, 21.22, 21.28, 22.84, 23.14, 55.58, 59.90, 59.97, 60.36, 104.18, 106.50, 127.07, 129.28, 136.24, 137.67, 138.27, 138.64, 150.91, 153.70, 155.56, 158.45, 165.70, 165.96. IR (cm^{-1}): 2977, 1699, 1615, 1507, 1237, 820, 698. MS (ESI) m/z $(M+H)^+$ Calcd $C_{30}H_{32}N_4O_4S$: 544.21. Found: 545.10.
Compound ***2c***: Yellow solid, mp 149–150 °C. ^{1}H NMR 400 MHz ($CDCl_3$): δ 1.04 (3H, t, J = 7 Hz, CH_3), 1.20 (3H, t, J = 7.1 Hz, CH_3), 2.32 (6H, s, CH_3), 3.34 (2H, s), 3.65 (2H, s), 3.82 (1H, s), 3.89 (1H, s), 3.96 (2H, q, J = 7.1 Hz, CH_2), 4.03 (2H, q, J = 7.1 Hz, CH_2), 5.89 (1H, s, CH), 6.30 (1H, s, NH), 6.64 (1H, d, J = 8.1 Hz, ArH), 6.79 (1H, d, J = 8.2 Hz, ArH), 6.84 (1H, d, J = 6.7 Hz, ArH), 6.85–6.94 (2H, m, ArH), 7.17–7.25 (2H, m, ArH), 7.27 (1H, d, J = 7.6 Hz, ArH). ^{13}C NMR 100 MHz ($CDCl_3$): δ 14.12, 14.18, 22.92, 23.07, 55.35, 59.99, 60.05, 101.94, 110.86, 110.95, 119.47, 119.68, 121.11, 121.33, 126.79, 129.28, 130.36, 157.63, 158.01, 159.22, 159.58, 165.97, 166.02, 166.10, 166.18. IR (cm^{-1}): 2982, 1694, 1610, 1504, 1230, 743, 691. MS (ESI) m/z $(M+H)^+$ Calcd $C_{30}H_{32}N_4O_6S$: 576.20. Found: 577.00
Compound ***2d***: Yellow solid, mp 104–105 °C. ^{1}H NMR 400 MHz ($CDCl_3$): δ 1.15 (3H, t, J = 7.2 Hz, CH_3), 1.21 (3H, t, J = 7.1 Hz, CH_3), 2.40 (6H, s, CH_3), 3.55 (3H, s, CH_3), 3.75 (3H, s, CH_3), 4.06 (2H, q, J = 7 Hz, CH_2), 4.14 (2H, q, J = 7.2 Hz, CH_2), 5.39 (1H, s, CH), 6.24 (1H, s, NH), 6.39 (1H, d, J = 6.7 Hz, ArH), 6.51 (1H, t, J = 6.7 Hz, ArH), 6.73 (1H, d, J = 8.1 Hz, ArH), 6.85 (1H, d, J = 8.2 Hz, ArH), 6.94–6.98 (2H, m, ArH), 7.01(1H, t, J = 6.7 Hz), 7.20 (1H, t, J = 7.9 Hz, ArH). ^{13}C NMR 100 MHz ($CDCl_3$): δ 14.16, 14.17, 22.92, 23.24, 54.98, 55.13, 55.67, 60.37, 103.67, 106.14, 112.54, 113.36, 114.39, 114.51, 119.23, 120.10, 129.40, 129.84, 140.65, 141.95, 150.48, 158.07, 159.40, 159.69, 165.63, 165.85. IR (cm^{-1}): 2980, 1703, 1600, 1511, 1226, 779, 698. MS (ESI) m/z $(M+H)^+$ Calcd $C_{30}H_{32}N_4O_6S$: 576.2; Found: 577
Compound ***2e***: Yellow solid, mp 154–156 °C. ^{1}H NMR 400 MHz ($CDCl_3$): δ 1.14 (3H, t, J = 7.1 Hz, CH_3), 1.21(3H, t, J = 7.1 Hz, CH_3), 2.39 (1H, s, CH_3), 2.43 (1H, s, CH_3), 3.73 (1H, s, CH_3), 3.83 (1H, s, OCH_3), 4.04 (2H, q, J = 7.1 Hz, CH_2), 4.11 (2H, q, J = 7 Hz, CH_2), 5.31 (1H, s, CH), 6.18 (1H, s, NH), 6.54 (2H, d, J = 6.7 Hz, ArH), 6.71 (2H, d, J = 6.7 Hz, ArH), 6.84 (2H, d, J = 6.8 Hz, ArH), 7.34 (2H, d, J = 6.8,

ArH). ^{13}C NMR 100 MHz ($CDCl_3$): δ 14 .17, 22.83, 23.10, 55.09, 55.25, 55.29, 59.67, 59.97, 60.34, 104.40, 106.52, 113.54, 113.89, 128.47, 129.51, 131.35, 132.92, 150.99, 153.74, 155.38, 158.37, 159.71, 159.77, 165.70, 165.97. IR (cm^{-1}): 2977, 1704, 1605, 1504, 1240, 830, 700. MS (ESI) m/z $(M+H)^+$ Calcd $C_{30}H_{32}N_4O_6S$: 576.20. Found: 577.05

Compound ***2f***: Yellow solid, mp 135–136 °C. ^{1}H NMR 400 MHz ($CDCl_3$): δ 1.16 (3H, t, J = 7.1 Hz, CH_3), 1.20 (3H, t, J = 7.1 Hz, CH_3), 2.43 (3H, s, CH_3), 2.45 (3H, s, CH_3), 3.46 (3H, s, OCH_3), 3.81 (6H, s, OCH_3), 3.87 (3H, s, CH_3), 4.09 (4H, q, J = 7.2 Hz, CH_2), 5.37 (1H, s, CH), 6.21 (1H, s, NH), 6.40–6.45 (2H, d, J = 7.2 Hz, ArH), 6.54 (1H, d, J = 8.1 Hz, ArH), 6.77 (1H, d, J = 8.3 Hz), 6.91 (2H, m, ArH), 7.12 (1H, t, J = 8.2 Hz, ArH). ^{13}C NMR 100 MHz ($CDCl_3$): δ 14.21, 22.90, 23.19, 55.38, 55.49, 55.73, 55.78, 59.91, 60.03, 60.38, 103.89, 106.14, 109.83, 110.61, 110.64, 111.80, 119.70, 120.41, 131.76, 133.22, 148.35, 149.07, 149.10, 149.39, 150.44, 155.37, 165.71, 165.97. IR (cm^{-1}): 2915, 1698, 1620, 1510, 1229, 853, 766, 686. MS (ESI) m/z $(M+H)^+$ Calcd $C_{32}H_{36}N_4O_8S$: 636.23. Found: 637.10

Compound ***2g***: Yellow solid, mp 138–140 °C. ^{1}H NMR 400 MHz ($CDCl_3$): δ 1.05 (3H, t, J = 7.1 Hz, CH_3), 1.20 (3H, t, J = 7 Hz, CH_3), 2.38 (3H, s, CH_3), 3.96 (2H, q, J = 7.2 Hz, CH_2), 4.09 (2H, q, J = 6.9 Hz, CH_2), 5.98 (1H, s, CH), 6.55 (1H, s, NH), 6.83 (1H, q, J = 7.5 Hz, ArH), 7.19 (1H,d, J = 8.2 Hz, ArH), 7.20–7.33 (5H, m, ArH), 7.33–7.46 (1H, m, ArH). ^{13}C NMR 100 MHz ($CDCl_3$): δ 14.00, 14.22, 22.56, 22.99, 53.73, 60.01, 60.42, 102.03, 127.17, 127.98, 128.25, 129.39, 129.71, 130.45, 130.62, 132.78, 136.68, 150.49, 153.30, 157.05, 158.62, 165.35, 165.50. IR (cm^{-1}): 2978, 1702, 1608, 1511, 1206, 780, 689.MS (ESI) m/z $(M+H)^+$ Calcd $C_{28}H_{26}Cl_2N_4O_4S$: 584.11. Found: 584.95.

Compound ***2h***: Yellow solid, mp 128–130 °C. ^{1}H NMR 400 MHz ($CDCl_3$): δ 1.11 (3H, t, J = 7.1 Hz, CH_3), 1.17 (3H, t, J = 7.1 Hz, CH_3), 2.37 (3H, s, CH_3), 2.42 (3H, s, CH_3), 4.02 (2H, q, J = 7 Hz, CH_2), 4.08 (2H, q, J = 7.2 Hz, CH_2), 5.45 (1H, s, CH), 6.16 (1H, s, NH), 7.23–7.33 (6H, m, ArH), 7.38–7.41 (2H, m, ArH). ^{13}C NMR 100 MHz ($CDCl_3$): δ 14.13, 14.09, 22.85, 23.25, 56.11, 59.68, 59.92, 60.01, 60.30, 102.71, 106.43, 127.10, 127.43, 128.09, 128.44, 128.75, 128.92, 129.15, 139.61, 140.06, 153.37, 156.32, 158.52, 165.49, 165.79. IR (cm^{-1}): 2980, 1707, 1606, 1504, 1230, 810, 686. MS (ESI) m/z $(M+H)^+$ Calcd $C_{28}H_{26}Cl_2N_4O_4S$: 584.11. Found: 584.95.

Compound ***2i***: Yellow solid, mp 133–134 °C. ^{1}H NMR 400 MHz ($CDCl_3$): δ 1.12 (3H, t, J = 7.1 Hz, CH_3), 1.18 (3H, t, J = 7.1 Hz, ArH), 2.40 (3H, s, CH_3), 2.44 (3H, s, CH_3), 4.04 (2H, q, J = 7 Hz, CH_2), 4.11 (2H, q, J = 7.4 Hz, CH2), 5.45 (1H, s, CH), 6.17 (1H, s, NH), 7.17–7.26 (3H, m, ArH), 7.37–7.47 (4H, m, ArH), 7.65 (1H, t, J = 7.4 Hz, ArH). ^{13}C NMR 100 MHz ($CDCl_3$): δ 14.11, 14.15, 22.96, 23.28, 55.70, 60.16, 60.50, 102.37, 105.87, 122.28, 123.19, 126.14, 127.01, 129.97, 130.51, 131.90, 131.92, 132.38, 141.70, 141.90, 148.64, 153.85, 156.63, 158.00, 165.19, 165.52. IR (cm^{-1}): 2974, 1701, 1605, 1493, 1232, 785, 665. MS (ESI) m/z $(M+H)^+$ Calcd $C_{28}H_{26}Br_2N_4O_4S$: 672.00. Found: 673.75.

Compound ***2j***: Yellow solid, mp 152–153 °C. ^{1}H NMR 400 MHz ($CDCl_3$): δ 1.11 (3H, t, J = 7.1 Hz, CH_3), 1.18 (3H, t, J = 7.1 Hz, CH_3), 2.36 (3H, s, CH_3), 2.42 (3H, s, CH_3), 4.02 (2H, q, J = 7.1 Hz, CH_2), 4.09 (2H, q, J = 7.1 Hz, CH_2), 5.44 (1H, s, CH), 6.15 (1H, s, NH), 7.19 (2H, d, J = 6.6 Hz, ArH), 7.34 (2H, d, J = 6.7 Hz, ArH), 7.43–7.49 (4H, m, ArH). ^{13}C NMR 100 MHz ($CDCl_3$): δ 14.11, 14.15, 22.91, 23.29, 55.57, 59.09, 60.12, 60.48, 102.60, 106.09, 122.99, 123.32, 129.09, 130.16, 131.49, 132.14, 138.44, 138.90, 148.78, 153.58, 156.26, 158, 03, 165.25, 165.56. IR (cm^{-1}): 2983, 1704, 1603, 1505, 1228, 816, 687. MS (ESI) m/z $(M+H)^+$ Calcd $C_{28}H_{26}Br_2N_4O_4S$: 672.00. Found: 673.80.