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# FACILE SYNTHESIS OF 2-ALKYLTHIO-5,6,7,8-TETRAHYDROBENZOTHIENO[2,3-*d*]-PYRIMIDIN-4(3*H*)-ONES

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***Isothiocyanate 2, obtained from aza-Wittig reaction of iminophosphorane 1 with $CS_2$, reacted with amine to give 2-thioxo-2,3,5,6,7,8-hexahydrobenzothieno[2,3-d]pyrimidin-4(1H)-ones 4 in the presence of sodium ethoxide. S-Alkylation of 4 produced 2-alkylthio-5,6,7,8-tetrahydrobenzothieno[2,3-d]pyrimidin-4(3H)-ones 5 in good yields.***

***Keywords***: Aza-Wittig reaction; carbon disulfide; iminophosphorane; isothiocyanate; thieno[2,3-*d*]-pyrimidin-4(3*H*)-one

Thienopyrimidines, which are well-known bioisosteres of quinazolines, are of great importance because of their remarkable biological properties. They show significant antifungal, antibacterial, antimalarial, and antiallergic activities.[1–5] Also 2-alkylthio-substituted thienopyrimidinones show significant angiotensin II receptor blocker or 5-$HT_{1A}$ receptor activities.[6,7] 2-Alkylthio-substituted thienopyrimidinones are generally synthesized from corresponding isothiocyanates (Scheme 1); however, the highly toxic thiophosgene was used to transfer 2-amino-thiophene-3-carboxylates into isothiocyanates in the synthetic route.[8–11]

The aza-Wittig reactions of functionalized iminophosphoranes with isocyanates or carbon disulfide were applied to produce carbodiimides or isothiocyanate able to undergo a plethora of heterocyclization reactions.[12–14] Recently, we have become interested in the preparation of *N*-heteroaryliminophosphoranes because these species are promising building blocks for the synthesis of nitrogen heterocycles.[15–20] As a continuation of our research for new biologically active heterocycles, we herein report a facile synthesis of 2-alkylthio-5,6,7,8-tetrahydrobenzothieno[2,3-*d*]pyrimidin-4(3*H*)-ones without using the highly toxic thiophosgene.

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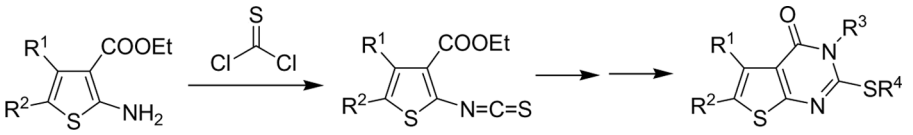
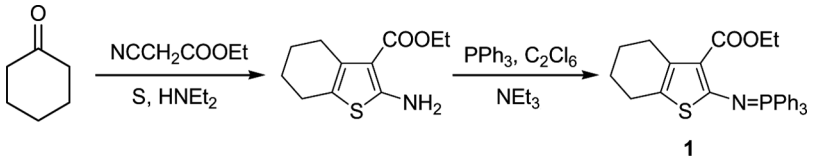


**Scheme 1.** Literature preparative route of 2-alkylthiothienopyrimidinones.

The tetrahydrobenzo[*b*]thiophene, easily obtained by the Gewald method from cyclohexanone, ethyl cyanoacetate, and sulfur, was converted to iminophosphorane **1** via reaction with triphenylphosphine, hexachloroethane, and triethylamine (Scheme 2).[21]

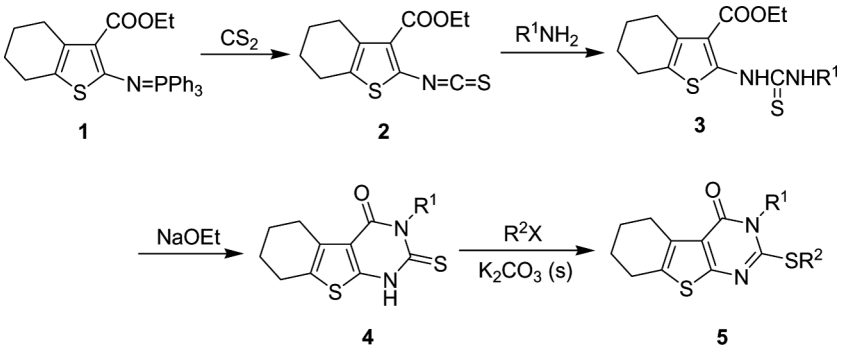
The iminophosphorane **1** reacted with excess carbon disulfide to give isothiocyanate **2**. However, the reaction was very slow at room temperature as determined by thin-layer chromatography (TLC). Good results were obtained when the reaction mixture was refluxed in a mixed solvent $CH_2Cl_2/CH_3CN$ (1:1) for 24 h under dry $N_2$ protection. Addition of the primary amines to the reaction mixture gave the thiourea intermediates **3**, which were further treated with sodium ethoxide to provide 2-thioxo-2,3,5,6,7,8-hexahydrobenzothieno[2,3-*d*]pyrimidin-4(1*H*)-ones **4** in 60–68% yields (Table 1). S-Alkylation of **4** with alkyl halides in the presence of potassium



**Scheme 2.** Preparation of iminophosphorane **1**.

**Table 1.** Preparation of compounds **4** and **5**

| No. | $R^1$ | $R^2X$ | Conditions | Yield (%) |
|---|---|---|---|---|
| **4a** | Pr | | rt, 2 h | 60 |
| **4b** | 2-$NH_2C_6H_4$ | | 40 °C, 6 h | 65 |
| **4c** | 4-$ClC_6H_4$ | | 50 °C, 6 h | 68 |
| **5a** | Pr | MeI | rt, 2 h | 75 |
| **5b** | Pr | PrBr | 40 °C, 2 h | 65 |
| **5c** | Pr | BuBr | 50 °C, 2 h | 78 |
| **5d** | Pr | $ClCH_2CN$ | 50 °C, 2 h | 67 |
| **5e** | Pr | $ClCH_2COOEt$ | 50 °C, 2 h | 92 |
| **5f** | 2-$NH_2C_6H_4$ | MeI | rt, 1 h | 80 |
| **5g** | 2-$NH_2C_6H_4$ | EtBr | 40 °C, 1 h | 78 |
| **5h** | 2-$NH_2C_6H_4$ | PrBr | 40 °C, 1 h | 74 |
| **5i** | 2-$NH_2C_6H_4$ | BuBr | 50 °C, 1 h | 73 |
| **5j** | 4-$ClC_6H_4$ | MeI | rt, 1 h | 85 |
| **5k** | 4-$ClC_6H_4$ | EtBr | 40 °C, 1 h | 83 |
| **5l** | 4-$ClC_6H_4$ | PrBr | 40 °C, 1 h | 90 |
| **5m** | 4-$ClC_6H_4$ | BuBr | 50 °C, 1 h | 79 |
| **5n** | 4-$ClC_6H_4$ | $PhCH_2Cl$ | 50 °C, 1 h | 93 |
| **5o** | 4-$ClC_6H_4$ | $ClCH_2COOEt$ | 50 °C, 1 h | 78 |




**Scheme 3.** Preparation of 2-alkylthiothienopyrimidinones.



carbonate provided 2-alkylthio-5,6,7,8-tetrahydrobenzothieno[2,3-*d*]pyrimidin-4(3*H*)-ones **5** in 65–93% yields. With an alkylation reagent such as $R^2I$, the alkylation could be carried out at room temperature. With other alkylation reagents, the alkylation had to be carried out at 40–50 °C (Scheme 3).

The structure of the synthesized compound **5** was confirmed by spectral data and elemental analyses. For example, the $^1H$ NMR spectral data of **5a** show the signals of $-NCH_2$ at 4.02 ppm as triplets, signals of $SCH_3$ at 2.60 ppm as singlets, and the signals of $CH_2CH_3$ at 1.81–1.74 ppm and 0.99 ppm as multiplets and triplets respectively. The cyclohexnyl ring's signals appeared at 2.99–2.71 ppm and 1.88–1.82 ppm as multiplets. The MS spectrum of **5a** shows a molecule ion peak ($M^+$) at m/z 294 with 100% abundance.

In conclusion, we have developed a facile synthesis of 2-alkylthio-5,6,7,8-tetrahydrobenzothieno[2,3-*d*]pyrimidin-4(3*H*)-ones starting from easily accessible materials without using the highly toxic thiophosgene.

## EXPERIMENTAL

Melting points were determined using an X-4 model apparatus and are uncorrected. Mass spectra (MS) were measured on a Finnigan Trace MS spectrometer. $^1H$ NMR spectra were recorded in $CDCl_3$ on a Varian Mercury 400 spectrometer, and resonances are given in ppm (δ) relative to tetramethylsilane (TMS). Elemental analyses were performed on a Vario EL III elementary analysis instrument.

### Preparation of 2-Thioxo-2,3,5,6,7,8-hexahydrobenzothieno-[2,3-*d*]pyrimidin-4(1*H*)-one 4

Excess carbon disulfide (15 mL) was added to a solution of iminophosphorane **1** (9.70 g, 20 mmol) in anhydrous methylene chloride and acetonitrile (20 mL, v/v = 1:1). After the reaction mixture was refluxed for 24 h under dry $N_2$ protection, the solvent was condensed under reduced pressure, and ether (10 mL) was added to precipitate triphenylphosphine sulfide. The precipitate was removed by filtration, and the filtrate was evaporated to give isothiocyanate **2**, which was used directly without further purification. Amine (20 mmol) was added to a solution of the crude **2** in

$CH_3CN$ (20 mL), and the mixture was stirred for 0.5–1 h at room temperature. After a catalytic amount of sodium ethoxide was added, the reaction mixture was stirred for 2–6 h at room temperature to 50 °C. The precipitated solid was collected, washed with ethanol, and recrystallized from methylene chloride/petroleum ether to give 2-thioxo-2,3,5,6,7,8-hexahydrobenzothieno[2,3-*d*]pyrimidin-4(1*H*)-ones **4**.

**Previously unreported 4b.** White solid, mp 250–252 °C, $^1$H NMR ($CDCl_3$, 400 MHz) δ 8.6 (s, 1H, NH), 7.32–6.84 (m, 4H, Ar-H), 3.05 (br, 2H, $NH_2$), 2.94–2.65 (m, 4H, $2CH_2$), 1.85–1.77 (m, 4H, $2CH_2$); MS m/z (%), 329 ($M^+$, 24), 315 (4), 267 (6), 174 (14), 149 (100), 132 (45), 117 (72). Elemental anal. calcd. for $C_{16}H_{15}N_3OS_2$: C, 58.33; H, 4.59; N, 12.76. Found: C, 58.54; H, 4.63; N, 12.59.



### Preparation of 2-Alkylthio-5,6,7,8-tetrahydrobenzothieno-[2,3-*d*]pyrimidin-4(3*H*)-ones 5

Alkyl halide (1 mmol) and solid potassium carbonate (0.28 g, 2 mmol) were added to a solution of 2-thioxo-2,3,5,6,7,8-hexahydrobenzothieno[2,3-*d*]pyrimidin-4(1*H*)-one **4** (1 mmol) in dry $CH_3CN$ (5 mL). The mixture was stirred for 1–2 h at room temperature or 40–50 °C and filtered. The filtrates was condensed, and the residue was recrystallized from methylene chloride/petroleum ether to give 2-alkylthio-5,6,7,8-tetrahydrobenzothieno[2,3-*d*]pyrimidin-4(3*H*)-ones **5a**–**5o**.

**2-Methylthio-3-propyl-5,6,7,8-tetrahydrobenzothieno[2,3-*d*]pyrimidin-4(3*H*)-one (5a).** White solid, mp 121–123 °C. $^1$H NMR ($CDCl_3$, 400 MHz): δ 4.02 (t, $J = 7.8$ Hz, 2H, $NCH_2$), 2.99–2.71 (m, 4H, $2CH_2$), 2.60 (s, 3H, $SCH_3$), 1.88–1.82 (m, 4H, $2CH_2$), 1.81–1.74 (m, 2H, $CH_2$), 0.99 (t, $J = 7.2$ Hz, 3H, $CH_3$). MS (m/z, %): 294 ($M^+$, 100), 279 (51), 252 (90), 224 (37), 205 (22), 179 (11), 133 (13). Elemental anal. calcd. for $C_{14}H_{18}N_2OS_2$: C, 57.11; H, 6.16; N, 9.51. Found: C, 57.34; H, 6.31; N, 9.59.

**3-Propyl-2-propylthio-5,6,7,8-tetrahydrobenzothieno[2,3-*d*]pyrimidin-4(3*H*)-one (5b).** White solid, mp 78–79 °C. $^1$H NMR ($CDCl_3$, 400 MHz): δ 4.03 (t, $J = 7.8$ Hz, 2H, $NCH_2$), 3.20 (t, $J = 7.2$ Hz, 2H, $SCH_2$), 2.97–2.74 (m, 4H, $2CH_2$), 1.86–1.74 (m, 8H, $4CH_2$), 1.06 (t, $J = 7.2$ Hz, 3H, $CH_3$), 1.00 (t, $J = 7.2$ Hz, 3H, $CH_3$). MS (m/z, %): 322 ($M^+$, 100), 280 (46), 239 (7). Elemental anal. calcd. for $C_{16}H_{22}N_2OS_2$: C, 59.59; H, 6.88; N, 8.69. Found: C, 59.44; H, 6.64; N, 8.86.

**2-Butylthio-3-propyl-5,6,7,8-tetrahydrobenzothieno[2,3-*d*]pyrimidin-4(3*H*)-one (5c).** White solid, mp 68–70 °C. $^1$H NMR ($CDCl_3$, 400 MHz): δ 4.03 (t, $J = 7.6$ Hz, 2H, $NCH_2$), 3.22 (t, $J = 7.2$ Hz, 2H, $SCH_2$), 2.99–2.72 (m, 4H, $2CH_2$), 1.87–1.48 (m, 10H, $5CH_2$), 1.02–0.95 (m, 6H, $2CH_3$). MS (m/z, %): 336 ($M^+$, 100), 279 (49), 238 (79), 178 (53), 150 (12). Elemental anal. calcd. for $C_{17}H_{24}N_2OS_2$: C, 60.68; H, 7.19; N, 8.32. Found: C, 60.72; H, 7.32; N, 8.26.

**2-(Cyanomethylene)thio-3-propyl-5,6,7,8-tetrahydrobenzothieno[2,3-*d*]pyrimidin-4(3*H*)-one (5d).** White solid, mp 189–190 °C. $^1$H NMR ($CDCl_3$, 400 MHz): δ 4.05 (s, 2H, $SCH_2$), 3.98 (t, $J = 7.6$ Hz, 2H, $NCH_2$), 2.99–2.74 (m, 4H, $2CH_2$), 1.89–1.77 (m, 6H, $3CH_2$), 1.01 (t, $J = 7.2$ Hz, 3H, $CH_3$). MS (m/z, %): 319

($M^+$, 100), 280 (77), 244 (22), 223 (13). Elemental anal. calcd. for $C_{15}H_{17}N_3OS_2$: C, 56.40; H, 5.36; N, 13.15. Found: C, 56.12; H, 5.48; N, 13.26.

**2-(Ethoxycarbonylmethylene)thio-3-propyl-5,6,7,8-tetrahydrobenzothieno-[2,3-*d*]pyrimidin-4(3*H*)-one (5e).** White solid, mp 94–95 °C. $^1$H NMR ($CDCl_3$, 400 MHz): δ 4.23 (q, $J = 7.2$ Hz, 2H, $OCH_2$), 4.04 (t, $J = 7.6$ Hz, 2H, $NCH_2$), 3.96 (s, 2H, $SCH_2$), 2.99–2.74 (m, 4H, $2CH_2$), 1.85–1.79 (m, 6H, $3CH_2$), 1.31 (t, $J = 7.2$ Hz, 3H, $CH_3$), 1.01 (t, $J = 7.2$ Hz, 3H, $CH_3$). MS (m/z, %): 366 ($M^+$, 100), 321 (14), 279 (59), 42 (11). Elemental anal. calcd. for $C_{17}H_{22}N_2O_3S_2$: C, 55.71; H, 6.05; N, 7.64. Found: C, 55.53; H, 6.21; N, 7.56.

**3-(2-Aminophenyl)-2-methylthio-5,6,7,8-tetrahydrobenzothieno[2,3-*d*]-pyrimidin-4(3*H*)-one (5f).** White solid, mp 234–235 °C. $^1$H NMR ($CDCl_3$, 400 MHz): δ 7.33–6.89 (m, 4H, Ar-H), 3.34 (br, 2H, $NH_2$), 2.96–2.75 (m, 4H, $2CH_2$), 2.48 (s, 3H, $SCH_3$), 1.91–1.80 (m, 4H, $2CH_2$). MS (m/z, %): 343 ($M^+$, 100), 326 (18), 295 (65), 267 (27), 254 (7), 117 (6). Elemental anal. calcd. for $C_{17}H_{17}N_3OS_2$: C, 59.45; H, 4.99; N, 12.23. Found: C, 59.68; H, 4.92; N, 12.35.

**3-(2-Aminophenyl)-2-ethylthio-5,6,7,8-tetrahydrobenzothieno[2,3-*d*]-pyrimidin-4(3*H*)-one (5g).** White solid, mp 159–160 °C. $^1$H NMR ($CDCl_3$, 400 MHz): δ 7.30–6.87 (m, 4H, Ar-H), 3.22 (br, 2H, $NH_2$), 3.11–3.08 (m, 2H, $SCH_2$), 2.97–2.75 (m, 4H, $2CH_2$), 1.89–1.80 (m, 4H, $2CH_2$), 1.31 (t, $J = 7.2$ Hz, 3H, $CH_3$). MS (m/z, %): 357 ($M^+$, 100), 341 (32), 295 (98), 267 (77), 254 (21), 118 (18). Elemental anal. calcd. for $C_{18}H_{19}N_3OS_2$: C, 60.47; H, 5.36; N, 11.75. Found: C, 60.59; H, 5.16; N, 11.84.

**3-(2-Aminophenyl)-2-propylthio-5,6,7,8-tetrahydrobenzothieno[2,3-*d*]-pyrimidin-4(3*H*)-one (5h).** White solid, mp 175–176 °C. $^1$H NMR ($CDCl_3$, 400 MHz): δ 7.33–6.88 (m, 4H, Ar-H), 3.20 (br, 2H, $NH_2$), 3.12–3.02 (m, 2H, $SCH_2$), 2.95–2.76 (m, 4H, $2CH_2$), 1.89–1.80 (m, 4H, $2CH_2$), 1.71–1.66 (m, 2H, $CH_2$), 0.99 (t, $J = 7.2$ Hz, 3H, $CH_3$). MS (m/z, %): 371 ($M^+$, 100), 354 (13), 296 (97), 267 (46), 90 (19). Elemental anal. calcd. for $C_{19}H_{21}N_3OS_2$: C, 61.42; H, 5.70; N, 11.31. Found: C, 61.59; H, 5.76; N, 11.24.

**3-(2-Aminophenyl)-2-butylthio-5,6,7,8-tetrahydrobenzothieno[2,3-*d*]-pyrimidin-4(3*H*)-one (5i).** White solid, mp 159–160 °C. $^1$H NMR ($CDCl_3$, 400 MHz): δ 7.33–6.88 (m, 4H, Ar-H), 3.20 (br, 2H, $NH_2$), 3.12–3.02 (m, 2H, $SCH_2$), 2.95–2.76 (m, 4H, $2CH_2$), 1.89–1.80 (m, 4H, $2CH_2$), 1.65–1.40 (m, 4H, $2CH_2$), 0.91 (t, $J = 7.2$ Hz, 3H, $CH_3$). MS (m/z, %): 385 ($M^+$, 100), 368 (11), 312 (22), 295 (85), 267 (27), 222 (20). Elemental anal. calcd. for $C_{20}H_{23}N_3OS_2$: C, 62.30; H, 6.01; N, 10.90. Found: C, 62.53; H, 5.83; N, 10.96.

**3-(4-Chlorophenyl)-2-methylthio-5,6,7,8-tetrahydrobenzothieno[2,3-*d*]-pyrimidin-4(3*H*)-one (5j).** White solid, mp > 300 °C. $^1$H NMR ($CDCl_3$, 400 MHz): δ 7.52–7.21 (m, 4H, Ar-H), 2.94–2.77 (m, 4H, $2CH_2$), 2.49 (s, 3H, $SCH_3$), 1.89–1.80 (m, 4H, $2CH_2$). MS (m/z, %): 362 ($M^+$, 100), 329 (21), 314 (31), 277 (93), 234 (12), 76 (13). Elemental anal. calcd. for $C_{17}H_{15}ClN_2OS_2$: C, 56.26; H, 4.17; N, 7.72. Found: C, 56.38; H, 4.24; N, 7.43.

**3-(4-Chlorophenyl)-2-ethylthio-5,6,7,8-tetrahydrobenzothieno[2,3-*d*]-pyrimidin-4(3*H*)-one (5k).** White solid, mp 211–212 °C. $^1$H NMR ($CDCl_3$, 400 MHz): δ 7.51–7.20 (m, 4H, Ar-H), 3.11 (q, $J = 7.2$ Hz, 2H, $SCH_2$), 2.94–2.75 (m, 4H, $2CH_2$), 1.89–1.80 (m, 4H, $2CH_2$), 1.31 (t, $J = 7.2$ Hz, 3H, $CH_3$). MS (m/z, %): 376 ($M^+$, 100), 347 (32), 295 (98), 267 (77), 254 (21), 149 (11), 90 (19). Elemental anal. calcd. for $C_{18}H_{17}ClN_2OS_2$: C, 57.36; H, 4.55; N, 7.43. Found: C, 57.23; H, 4.66; N, 7.49.

**3-(4-Chlorophenyl)-2-propylthio-5,6,7,8-tetrahydrobenzothieno[2,3-*d*]-pyrimidin-4(3*H*)-one (5l).** White solid, mp 204–205 °C. $^1$H NMR ($CDCl_3$, 400 MHz): δ 7.51–7.20 (m, 4H, Ar-H), 3.09 (t, $J = 7.2$ Hz, 2H, $SCH_2$), 2.93–2.76 (m, 4H, $2CH_2$), 1.88–1.82 (m, 4H, $2CH_2$), 1.71–1.65 (m, 2H, $CH_2$), 0.99 (t, $J = 7.2$ Hz, 3H, $CH_3$). MS (m/z, %): 390 ($M^+$, 100), 357 (32), 315 (19), 42 (19). Elemental anal. calcd. for $C_{19}H_{19}ClN_2OS_2$: C, 58.37; H, 4.90; N, 7.17. Found: C, 58.13; H, 4.96; N, 7.24.

**3-(4-Chlorophenyl)-2-butylthio-5,6,7,8-tetrahydrobenzothieno[2,3-*d*]-pyrimidin-4(3*H*)-one (5m).** White solid, mp 180–181 °C. $^1$H NMR ($CDCl_3$, 400 MHz): δ 7.51–7.20 (m, 4H, Ar-H), 3.11 (t, $J = 7.2$ Hz, 2H, $SCH_2$), 2.94–2.75 (m, 4H, $2CH_2$), 1.89–1.80 (m, 4H, $2CH_2$), 1.64–1.37 (m, 4H, $2CH_2$), 0.92 (t, $J = 7.2$ Hz, 3H, $CH_3$). MS (m/z, %): 404 ($M^+$, 100), 348 (45), 315 (15), 56 (12). Elemental anal. calcd. for $C_{20}H_{21}ClN_2OS_2$: C, 59.32; H, 5.23; N, 6.92. Found: C, 59.23; H, 5.26; N, 6.74.

**3-(4-Chlorophenyl)-2-(phenylmethylene)thio-5,6,7,8-tetrahydroben-zothieno[2,3-*d*]pyrimidin-4(3*H*)-one (5n).** White solid, mp 201–202 °C. $^1$H NMR ($CDCl_3$, 400 MHz): δ 7.47–7.19 (m, 9H, Ar-H), 4.35 (s, 2H, $SCH_2$), 2.94–2.76 (m, 4H, $2CH_2$), 1.89–1.80 (m, 4H, $2CH_2$). MS (m/z, %): 438 ($M^+$, 100), 405 (52), 329 (11), 315 (19), 284 (29), 91 (27). Elemental anal. calcd. for $C_{22}H_{17}ClN_2OS_2$: C, 62.93; H, 4.36; N, 6.38. Found: C, 62.77; H, 4.11; N, 6.42.

**3-(4-Chlorophenyl)-2-(ethoxycarbonylmethylene)thio-5,6,7,8-tetrahy-drobenzothieno[2,3-*d*]pyrimidin-4(3*H*)-one (5o).** White solid, mp 211–213 °C. $^1$H NMR ($CDCl_3$, 400 MHz): δ 7.53–7.25 (m, 4H, Ar-H), 4.21 (q, $J = 7.2$ Hz, 2H, $OCH_2$), 3.85 (s, 2H, $SCH_2$), 2.93–2.74 (m, 4H, $2CH_2$), 1.88–1.79 (m, 4H, $2CH_2$), 1.30 (t, $J = 7.2$ Hz, 3H, $CH_3$). MS (m/z, %): 434 ($M^+$, 100), 388 (16), 361(31), 315 (16), 108 (72). Elemental anal. calcd. for $C_{20}H_{19}ClN_2O_3S_2$: C, 55.23; H, 4.40; N, 6.44. Found: C, 55.37; H, 4.32; N, 6.32.

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