A Convenient Synthesis of New Types of Benzodiazepine Derivatives: 2-Alkylsulfanyl-3*H*-4,5-dihydro-1,3-benzodiazepin-4-ones and 2-Alkylsulfanyl-3*H*-4,5-dihydro-1,3-benzodiazepine-4-thiones

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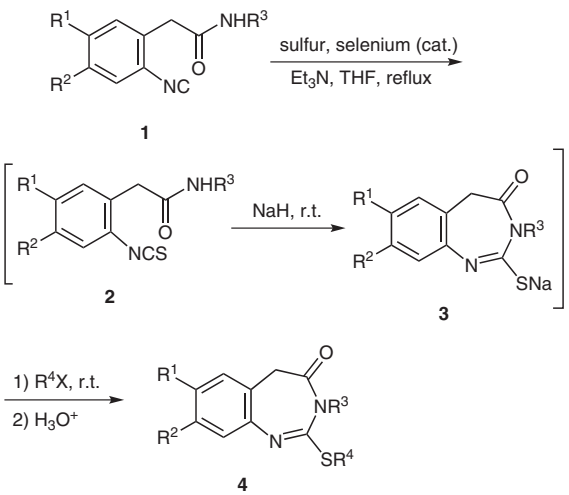
Abstract: An efficient method for preparing 2-alkylsulfanyl-3*H*-4,5-dihydro-1,3-benzodiazepin-4-ones and 2-alkylsulfanyl-3*H*-4,5-dihydro-1,3-benzodiazepine-4-thiones under mild conditions has been developed. Thus, 2-(2-isocyanophenyl)acetamides and 2-(2-isocyanophenyl)thioacetamides, easily available from respective 1-isocyano-2-methylbenzenes, were converted into the corresponding isothiocyanates on treatment with sulfur in the presence of a catalytic amount of selenium, which were then reacted with an equimolar amount to sodium hydride to give 2-(sodiosulfanyl)-3*H*-4,5-dihydro-1,3-benzodiazepin-4-one and 2-(sodiosulfanyl)-3*H*-4,5-dihydro-1,3-benzodiazepine-4-thione intermediates, respectively. These intermediates were allowed to react with various alkyl halides to afford the desired benzodiazepinone or benzodiazepinethione derivatives in a one-pot reaction.

Key words: benzodiazepines, isocyanides, isothiocyanates, sulfur, cyclization

The benzodiazepine skeletons, such as 3*H*-1,4-benzodiazepine[1] and 2,3-benzodiazepine,[2] are found in many biologically active compounds. Therefore, 3*H*-4,5-dihydro-1,3-benzodiazepine derivatives are also of potential biological importance. However, few practical methods for the preparation of 3*H*-4,5-dihydro-1,3-benzodiazepine derivatives are known, though Ito et al. have reported the formation of two 3*H*-4,5-dihydro-1,3-benzodiazepin-4-ones, as by-products in the preparation of indole-3-carboxamides from 2-(2-isocyanophenyl)acetamide derivatives.[3] In this report, we wish to describe a facile one-pot procedure for the synthesis of 2-alkylsulfanyl-3*H*-4,5-dihydro-1,3-benzodiazepin-4-ones **4** and 2-alkylsulfanyl-3*H*-4,5-dihydro-1,3-benzodiazepine-4-thiones **8** from secondary 2-(2-isocyanophenyl)acetamides **1** and 2-(2-isocyanophenyl)thioacetamides **5**, respectively. This is the first report on the synthesis of these types of benzodiazepine derivatives.

The one-pot synthesis of 2-alkylsulfanyl-3*H*-4,5-dihydro-1,3-benzodiazepin-4-one derivatives **4** was conducted by the process illustrated in Scheme 1. The starting precursors 2-(2-isocyanophenyl)acetamides **1** were prepared from respective 1-isocyano-2-methylbenzenes according to the procedure reported by Ito et al.[3] The 2-(2-isocyanophenyl)acetamides **1** were converted into the corresponding isothiocyanates **2** on treatment with sulfur in the presence of a catalytic amount of selenium and triethylamine in tetrahydrofuran at reflux temperature,[4] which were then treated with an equimolar amounts of sodium hydride at room temperature to afford 2-sodiosulfanyl-3*H*-4,5-dihydro-1,3-benzodiazepin-4-ones **3**. These intermediates were allowed to react with an equimolar amount of alkyl halide, such as methyl iodide, benzyl bromide, *tert*-butyl bromoacetate, 4-(bromomethyl)benzonitrile, 2-bromoacetonitrile, (4-nitrophenyl)methyl bromide, at the same temperature. The S-alkylation proceeded smoothly and highly selectively. The progress of each step of the sequence could be monitored by TLC (silica gel) analyses. The usual aqueous workup and subsequent purification by column chromatography on silica gel afforded the desired products **4**. The results summarized in Table 1 indicate that the yields are generally fair independent of the substituents on the benzene nuclei and N-substituents of the starting materials **1** and alkyl halides used.



Scheme 1 Preparation of 1,3-benzodiazepin-4-ones **4**

We also found that 2-alkylsulfanyl-3*H*-4,5-dihydro-1,3-benzodiazepine-4-thiones **8** could be similarly prepared in one-pot from 2-(2-isocyanophenyl)thioacetamides **5**, as illustrated in Scheme 2. The starting precursors 2-(2-isocyanophenyl)thioacetamides **5** were prepared from respective 1-isocyano-2-methylbenzenes according to the

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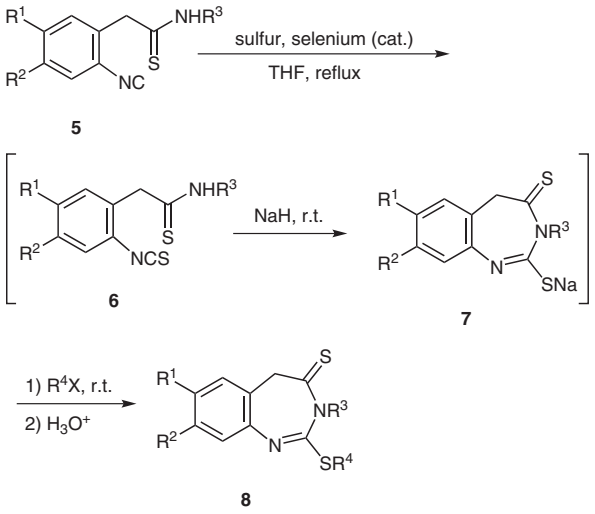
Table 1 Preparation of 3*H*-4,5-Dihydro-1,3-benzodiazepin-4-ones **4**

Entry	**1**	R^4X	**4** (Yield, %)[a]
1	**1a** ($R^1 = R^2 = H$, $R^3 = Ph$)	MeI	**4a** (69)
2	**1a**	BnBr	**4b** (63)
3	**1a**	*t*-BuO_2CCH_2Br	**4c** (65)
4	**1b** ($R^1 = R^2 = H$, R^3 = 3-Cl,4-MeC_6H_3)	MeI	**4d** (70)
5	**1c** ($R^1 = H$, $R^2 = Me$, $R^3 = n$-Bu)	4-$CNC_6H_4CH_2Br$	**4e** (70)
6	**1d** ($R^1 = Cl$, $R^2 = H$, $R^3 = t$-Bu)	$BrCH_2CN$	**4f** (68)
7	**1e** ($R^1 = MeO$, $R^2 = H$, R^3 = 4-ClC_6H_4)	4-$NO_2C_6H_4CH_2Br$	**4g** (71)

[a] Isolated yields.



Scheme 2 Preparation of 1,3-benzodiazepine-4-thiones **8**

procedure reported by Ito et al.[3] First, conversion of 2-(2-isocyanophenyl)thioacetamides **5** into the corresponding isothiocyanates **6** was attempted under the same conditions as described for the conversion of 2-(2-isocyanophenyl)acetamides **1** into the corresponding isothiocyanates **2**. However, each of the reactions resulted in the formation of an intractable mixture of products. Presumably, initially formed isothiocyanates were further converted into other complicated products in the presence of the relatively strong base, triethylamine. It was found that when triethylamine was omitted, the desired isothiocyanates **6** were formed cleanly; here the thioamide function may work as a weak base. These isothiocyanates were then treated successively with sodium hydride and various alkyl halides to give the desired benzodiazepine-4-thiones **8**, via the 2-sodiosulfanyl-3*H*-4,5-dihydro-1,3-benzodiazepine-4-thiones **7**. The results summarized in Table 2 indicate that the yields are also generally fair independent on the substituents on the benzene nuclei and N-substituents of the starting materials **4** and alkyl halides used.

Table 2 Preparation of 3*H*-4,5-Dihydro-1,3-benzodiazepine-4-thiones **8**

Entry	**5**	R^4X	**8** (Yield, %)[a]
1	**5a** ($R^1 = R^2 = H$, $R^3 = Ph$)	MeI	**8a** (69)
2	**5a**	EtBr	**8b** (59)
3	**5a**	BnBr	**8c** (64)
4	**5b** ($R^1 = H$, $R^2 = Me$, R^3 = 2-ClC_6H_4)	MeI	**8d** (67)
5	**5c** ($R^1 = MeO$, $R^2 = H$, $R^3 = Et$)	MeI	**8e** (61)
6	**5c**	CH_2=$CHCH_2Br$	**8f** (68)
7	**5c**	$BrCH_2CN$	**8g** (60)

[a] Isolated yields.

In conclusion, 2-(2-isocyanophenyl)acetamides **1** and 2-(2-isocyanophenyl)thioacetamides **5** have been utilized for the one-pot construction of new types of benzodiazepine skeletons, 2-alkylsulfanyl-3*H*-4,5-dihydro-1,3-benzodiazepin-4-ones **4** and 2-alkylsulfanyl-3*H*-4,5-dihydro-1,3-benzodiazepine-4-thiones **8**, respectively, via the corresponding isothiocyanates **2** and **6**, respectively. The present method may find value in organic synthesis because of its advantages: i) simplicity of the procedure, ii) milder reaction conditions, and iii) ready availability of the starting materials.

All melting points were obtained on a Laboratory Devices MEL-TEMP II melting apparatus and are uncorrected. IR spectra were determined with a Shimadzu FTIR-8300 spectrophotometer. The ^1H NMR spectra were determined in $CDCl_3$ using TMS as an internal reference with a JEOL ECP500 FT NMR spectrometer operating at 500 or a JEOL LA400 FT NMR spectrometer operating at 400 MHz. The ^{13}C NMR spectra were determined in $CDCl_3$ using TMS as an internal reference with a JEOL ECP500 FT NMR spectrometer operating at 125 MHz. Low-resolution MS spectra (EI, 70 eV) were measured by a JEOL JMS AX505 HA spectrometer. TLC was carried out on a Merck Kieselgel 60 PF_{254}. Column chromatography was performed using Merck Kieselgel 60 (0.063–0.200 mm). All of the organic solvents used in this study were dried over appropriate drying agents and distilled prior to use. 1-Isocyano-2-methylbenzenes were prepared according to the procedure reported previously by Ito et al.[5] All other chemicals used in this study were commercially available.

2-(2-Isocyanophenyl)acetamides 1

These compounds were prepared by treating the respective 1-isocyano-2-(lithiomethyl)benzenes, generated from 1-isocyano-2-methylbenzenes, with isocyanates according to the procedure reported by Ito et al.[3]

2-(2-Isocyanophenyl)-*N*-phenylacetamide (1a)[3]

Yield: 50%; white solid; $R_f = 0.23$ (THF–hexane, 1:4); mp 137–138 °C (hexane–CH_2Cl_2).

IR (KBr): 3275, 2126, 1665 cm^{-1}.

^{1}H NMR (500 MHz): δ = 3.86 (s, 2 H), 7.12 (t, *J* = 7.3 Hz, 1 H), 7.30 (s, 1 H), 7.31 (d, *J* = 7.8 Hz, 1 H), 7.32 (t, *J* = 7.8 Hz, 1 H), 7.36 (t, *J* = 7.8 Hz, 1 H), 7.43 (t, *J* = 7.3 Hz, 2 H), 7.50 (d, *J* = 7.8 Hz, 1 H), 7.51 (t, *J* = 7.3 Hz, 2 H).

Anal. Calcd for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86. Found: C, 76.10; H, 5.15; N, 11.80.

_N_-(3-Chloro-4-methylphenyl)-2-(2-isocyanophenyl)acetamide (1b)

Yield: 47%; pale-yellow solid; R_f = 0.25 (THF–hexane, 1:3); mp 160–162 °C (hexane–$CHCl_3$).

IR (KBr): 3269, 2124, 1663 cm^{-1}.

^{1}H NMR (500 MHz): δ = 2.31 (s, 3 H), 3.84 (s, 2 H), 7.14 (d, *J* = 8.3 Hz, 1 H), 7.24 (dd, *J* = 8.3, 2.3 Hz, 1 H), 7.32 (s, 1 H), 7.36 (td, *J* = 7.3, 1.4 Hz, 1 H), 7.42–7.44 (m, 2 H), 7.50 (dd, *J* = 7.3, 1.4 Hz, 1 H), 7.60 (d, *J* = 2.3 Hz, 1 H).

Anal. Calcd for $C_{16}H_{13}ClN_2O$: C, 67.49; H, 4.60; N, 9.84. Found: C, 67.28; H, 4.68; N, 9.79.

_N_-Butyl-2-(2-isocyano-4-methylphenyl)acetamide (1c)

Yield: 70%; yellow solid; R_f = 0.47 (THF–hexane, 1:3); mp 63–64 °C (hexane–Et_2O).

IR (KBr): 3295, 2118, 1645 cm^{-1}.

^{1}H NMR (400 MHz): δ = 0.90 (t, *J* = 7.3 Hz, 3 H), 1.31 (sext, *J* = 7.3 Hz, 2 H), 1.47 (quint, *J* = 7.3 Hz, 2 H), 2.34 (s, 3 H), 3.25 (q, *J* = 7.3 Hz, 2 H), 3.61 (s, 2 H), 5.52 (s, 1 H), 7.19 (d, *J* = 7.8 Hz, 1 H), 7.20 (s, 1 H), 7.31 (d, *J* = 7.8 Hz, 1 H).

Anal. Calcd for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.88; N, 12.16. Found: C, 72.95; H, 7.98; N, 12.10.

2-(5-Chloro-2-isocyanophenyl)-_N_-(1,1-dimethylethyl)acetamide (1d)

Yield: 45%; white solid; R_f = 0.26 (THF–hexane, 1:5); mp 149–150 °C (hexane–Et_2O).

IR (KBr): 3298, 2126, 1643 cm^{-1}.

^{1}H NMR (500 MHz): δ = 1.37 (s, 9 H), 3.54 (s, 2 H), 5.48 (br s, 1 H), 7.29 (dd, *J* = 8.7, 2.3 Hz, 1 H), 7.32 (d, *J* = 8.7 Hz, 1 H), 7.43 (d, *J* = 2.3 Hz, 1 H).

Anal. Calcd for $C_{13}H_{15}ClN_2O$: C, 62.28; H, 6.03; N, 11.17. Found: C, 62.28; H, 6.09; N, 11.13.

_N_-(4-Chlorophenyl)-2-(2-isocyano-5-methoxyphenyl)acetamide (1e)

Yield: 41%; pale-yellow solid; R_f = 0.21 (THF–hexane, 1:3); mp 162–163 °C (hexane–$CHCl_3$).

IR (KBr): 3279, 2120, 1655 cm^{-1}.

^{1}H NMR (500 MHz): δ = 3.79 (s, 2 H), 3.84 (s, 3 H), 6.84 (dd, *J* = 8.7, 2.7 Hz, 1 H), 6.98 (d, *J* = 2.7 Hz, 1 H), 7.27 (d, *J* = 8.7 Hz, 2 H), 7.36 (d, *J* = 8.7 Hz, 1 H), 7.39 (s, 1 H), 7.45 (d, *J* = 8.7 Hz, 2 H).

Anal. Calcd for $C_{16}H_{13}ClN_2O_2$: C, 63.90; H, 4.36; N, 9.31. Found: C, 63.85; H, 4.43; N, 9.27.

2-Methylsulfanyl-3-phenyl-3*H*-4,5-dihydro-1,3-benzodiazepin-4-one (4a); Typical Procedure

A mixture of **1a** (0.10 g, 0.42 mmol), Et_3N (0.11 g, 1.1 mmol), sulfur (16 mg, 0.51 mmol), and selenium (1.0 mg, 13 μmol) in THF (3 mL) was stirred at reflux temperature for 10 min. After cooling to r.t., NaH (60% in oil; 20 mg, 0.51 mmol) was added and the mixture was stirred for 30 min at the same temperature. MeI (72 mg, 0.51 mmol) was then added using a microsyringe and the stirring was continued for an additional 20 min before sat. aq NH_4Cl (10 mL) was added. During the reaction, the progress of each step was monitored by TLC (silica gel) analyses. The organic materials were extracted with EtOAc (3 × 10 mL), and the combined extracts were washed with brine (15 mL), dried (Na_2SO_4), and concentrated by evaporation. The residue was purified by column chromatography on silica gel to afford a crude solid, which was recrystallized to give pure **4a** as colorless crystals; yield: 82 mg (69%); mp 112–113 °C (hexane–Et_2O); R_f = 0.43 (EtOAc–hexane, 1:4).

IR (KBr): 1701, 1610 cm^{-1}.

^{1}H NMR (500 MHz): δ = 2.45 (s, 3 H), 3.66 (s, 2 H), 7.17 (dd, *J* = 7.3, 1.4 Hz, 1 H), 7.23 (td, *J* = 7.3, 1.4 Hz, 1 H), 7.28 (t, *J* = 7.8 Hz, 2 H), 7.36–7.42 (m, 5 H).

^{13}C NMR: δ = 15.81, 41.87, 123.99, 125.07, 126.33, 128.40, 128.57, 128.64, 128.67, 129.09, 138.02, 143.86, 153.16, 168.66.

MS: *m*/*z* (%) = 282 (100, [M$^+$]).

Anal. Calcd for $C_{16}H_{14}N_2OS$: C, 68.06; H, 5.00; N, 9.92. Found: C, 67.96; H, 5.19; N, 9.84.

3-Phenyl-2-(phenylmethyl)sulfanyl-3*H*-4,5-dihydro-1,3-benzodiazepin-4-one (4b)

Pale-yellow solid; R_f = 0.50 (EtOAc–hexane, 1:3); mp 107–109 °C (hexane–Et_2O).

IR (KBr): 1703, 1611 cm^{-1}.

^{1}H NMR (500 MHz): δ = 3.62 (s, 2 H), 4.28 (s, 2 H), 7.12 (dd, *J* = 7.3, 2.3 Hz, 2 H), 7.23–7.40 (m, 12 H).

^{13}C NMR: δ = 37.19, 41.88, 123.90, 125.12, 126.43, 127.29, 128.40 (2 C), 128.56, 128.59, 128.64, 129.05, 129.10, 136.71, 137.72, 143.73, 151.81, 168.55.

MS: *m*/*z* (%) = 358 (100, [M$^+$]).

Anal. Calcd for $C_{22}H_{18}N_2OS$: C, 73.71; H, 4.57; N, 8.47. Found: C, 73.60; H, 4.78; N, 8.42.

1,1-Dimethylethyl 2-(4-Oxo-3-phenyl-3*H*-4,5-dihydro-1,3-benzodiazepin-2-yl)sulfanylacetate (4c)

Pale-yellow needles; R_f = 0.42 (EtOAc–hexane, 1:3); mp 122–124 °C (hexane–CH_2Cl_2).

IR (KBr): 1709, 1614 cm^{-1}.

^{1}H NMR (500 MHz): δ = 1.42 (s, 9 H), 3.65 (s, 2 H), 3.72 (s, 2 H), 7.20 (dd, *J* = 7.8, 1.4 Hz, 1 H), 7.21 (t, *J* = 7.8 Hz, 1 H), 7.24–7.27 (m, 2 H), 7.36 (t, *J* = 7.8 Hz, 1 H), 7.38–7.42 (m, 4 H).

^{13}C NMR: δ = 27.97, 36.17, 41.86, 81.97, 124.00, 124.99, 126.54, 128.37, 128.58, 128.70, 128.88, 129.17, 137.58, 143.46, 151.08, 167.58, 168.56.

MS: *m*/*z* (%) = 382 (16, [M$^+$]), 326 (100).

Anal. Calcd for $C_{21}H_{22}N_2O_3S$: C, 65.95; H, 5.80; N, 7.32. Found: C, 65.90; H, 5.85; N, 7.23.

3-(3-Chloro-4-methylphenyl)-2-methylsulfanyl-3*H*-4,5-dihydro-1,3-benzodiazepin-4-one (4d)

Pale-yellow oil; R_f = 0.43 (THF–hexane, 1:5).

IR (neat): 1705, 1614 cm^{-1}.

^{1}H NMR (500 MHz): δ = 2.38 (s, 3 H), 2.46 (s, 3 H), 3.64 (s, 2 H), 7.00 (dd, *J* = 8.2, 2.3 Hz, 1 H), 7.15 (d, *J* = 2.3 Hz, 1 H), 7.23 (ddd, *J* = 8.2, 7.8, 1.4 Hz, 1 H), 7.24–7.28 (m, 2 H), 7.29 (d, *J* = 8.2 Hz, 1 H), 7.38 (ddd, *J* = 8.2, 7.8, 1.4 Hz, 1 H).

^{13}C NMR: δ = 15.81, 19.87, 41.79, 124.08, 124.89, 126.44, 126.95, 128.48, 128.59, 129.11, 131.12, 134.60, 136.54, 136.98, 143.75, 152.65, 168.68.

MS: *m*/*z* (%) = 330 (100, [M$^+$]).

Anal. Calcd for $C_{17}H_{15}ClN_2OS$: C, 61.72; H, 4.57; N, 8.47. Found: C, 61.71; H, 4.79; N, 8.31.

4-[(3-Butyl-8-methyl-4-oxo-3*H*-4,5-dihydro-1,3-benzodiazepin-2-yl)sulfanylmethyl]benzonitrile (4e)
Pale-yellow oil; R_f = 0.29 (THF–hexane, 1:5).

IR (neat): 2230, 1694, 1593 cm^{-1}.

^1H NMR (500 MHz): δ = 0.78 (t, *J* = 7.3 Hz, 3 H), 1.09 (sext, *J* = 7.3 Hz, 2 H), 1.40 (quint, *J* = 7.3 Hz, 2 H), 2.36 (s, 3 H), 3.35 (br s, 2 H), 3.71 (br s, 2 H), 4.39 (s, 2 H), 6.92 (s, 1 H), 7.01 (dd, *J* = 7.8, 1.4 Hz, 1 H), 7.10 (d, *J* = 7.8 Hz, 1 H), 7.56 (d, *J* = 8.7 Hz, 2 H), 7.63 (d, *J* = 8.7 Hz, 2 H).

^{13}C NMR: δ = 13.51, 19.55, 21.11, 30.69, 35.76, 41.20, 45.96, 111.18, 118.63, 122.45, 123.61, 127.41, 128.06, 129.85, 132.20, 138.16, 143.20 (2 C), 151.63, 168.59.

MS: *m*/*z* (%) = 377 (100, $[M^+]$).

Anal. Calcd for $C_{22}H_{23}N_3OS$: C, 70.00; H, 6.14; N, 11.13. Found: C, 69.85; H, 6.15; N, 11.35.

2-{[7-Chloro-4-oxo-3-(1,1-dimethylethyl)-3*H*-4,5-dihydro-1,3-benzodiazepin-2-yl]sulfanyl}acetonitrile (4f)
Colorless crystals; R_f = 0.20 (THF–hexane, 1:5); mp 156–158 °C (hexane–Et_2O).

IR (KBr): 2249, 1690, 1603 cm^{-1}.

^1H NMR (500 MHz): δ = 1.44 (s, 9 H), 3.32 (d, *J* = 14.2 Hz, 1 H), 3.36 (d, *J* = 14.2 Hz, 1 H), 3.77 (d, *J* = 16.5 Hz, 1 H), 4.01 (d, *J* = 16.5 Hz, 1 H), 7.14 (d, *J* = 8.7 Hz, 1 H), 7.23 (d, *J* = 2.3 Hz, 1 H), 7.32 (dd, *J* = 8.7, 2.3 Hz, 1 H).

^{13}C NMR: δ = 17.97, 28.90, 42.95, 59.79, 115.32, 123.67, 127.85, 128.21, 128.56, 131.58, 142.25, 153.23, 172.14.

MS: *m*/*z* (%) = 321 (78, $[M^+]$), 265 (100).

Anal. Calcd for $C_{15}H_{16}ClN_2OS$: C, 55.98; H, 5.01; N, 13.06. Found: C, 55.90; H, 5.00; N, 13.02.

3-(4-Chlorophenyl)-7-methoxy-2-(4-nitrophenylmethyl)sulfanyl-3*H*-4,5-dihydro-1,3-benzodiazepin-4-one (4g)
Yellow solid; R_f = 0.60 (THF–hexane, 1:1); mp 157–159 °C (hexane–CH_2Cl_2).

IR (KBr): 1703, 1614, 1520, 1346 cm^{-1}.

^1H NMR (500 MHz): δ = 3.53 (s, 2 H), 3.82 (s, 3 H), 4.31 (s, 2 H), 6.77 (d, *J* = 3.2 Hz, 1 H), 6.94 (dd, *J* = 8.7, 3.2 Hz, 1 H), 7.04 (d, *J* = 8.7 Hz, 2 H), 7.14 (d, *J* = 8.7 Hz, 1 H), 7.35 (d, *J* = 8.7 Hz, 2 H), 7.51 (d, *J* = 8.7 Hz, 2 H), 8.15 (d, *J* = 8.7 Hz, 2 H).

^{13}C NMR: δ = 36.23, 42.16, 55.70, 112.81, 115.20, 123.69, 125.31, 125.77, 129.53, 129.98, 130.00, 134.94, 136.12, 137.11, 145.15, 147.23, 148.48, 158.81, 168.11.

MS: *m*/*z* (%) = 467 (100, $[M^+]$).

Anal. Calcd for $C_{23}H_{18}ClN_3O_4S$: C, 59.04; H, 3.88; N, 8.98. Found: C, 59.04; H, 4.15; N, 8.95.

2-(2-Isocyanophenyl)thioacetamides 5
These compounds were prepared by treating the respective 1-isocyano-2-(lithiomethyl)benzenes with isothiocyanates according to the procedure reported by Ito et al.[3]

2-(2-Isocyanophenyl)-*N*-phenylthioacetamide (5a)[3]
Yield: 82%; pale-yellow solid; R_f = 0.25 (THF–hexane, 1:7); mp 93–95 °C (hexane–Et_2O).

IR (KBr): 3242, 2120, 1597 cm^{-1}.

^1H NMR (500 MHz): δ = 4.32 (s, 2 H), 7.28 (d, *J* = 7.8 Hz, 1 H), 7.36–7.47 (m, 5 H), 7.59 (d, *J* = 7.8 Hz, 1 H), 7.67 (d, *J* = 8.2 Hz, 2 H), 8.82 (s, 1 H).

Anal. Calcd for $C_{15}H_{12}N_2S$: C, 71.40; H, 4.79; N, 11.10. Found: C, 71.34; H, 4.84; N, 11.06.

***N*-(2-Chlorophenyl)-2-(2-isocyano-4-methylphenyl)thioacetamide (5b)**
Yield: 76%; yellow needle; R_f = 0.26 (THF–hexane, 1:4); mp 88–90 °C (hexane–Et_2O).

IR (KBr): 3219, 2120, 1591 cm^{-1}.

^1H NMR (500 MHz): δ = 2.38 (s, 3 H), 4.36 (s, 2 H), 7.20 (td, *J* = 7.8, 1.4 Hz, 1 H), 7.25–7.28 (m, 2 H), 7.31 (td, *J* = 8.2, 1.4 Hz, 1 H), 7.41 (d, *J* = 7.8 Hz, 1 H), 7.44 (d, *J* = 7.8 Hz, 1 H), 8.52 (d, *J* = 8.2 Hz, 1 H), 8.81 (s, 1 H).

Anal. Calcd for $C_{16}H_{13}ClN_2S$: C, 63.89; H, 4.36; N, 9.31. Found: C, 63.79; H, 4.56; N, 9.46.

***N*-Ethyl-2-(2-isocyano-5-methoxyphenyl)thioacetamide (5c)**
Yield: 80%; yellow solid; R_f = 0.28 (THF–hexane, 1:2); mp 59–62 °C (hexane–Et_2O).

IR (KBr): 3217, 2114, 1610 cm^{-1}.

^1H NMR (500 MHz): δ = 1.27 (t, *J* = 7.3 Hz, 3 H), 3.69 (q, *J* = 7.3 Hz, 1 H), 3.70 (q, *J* = 7.3 Hz, 1 H), 3.84 (s, 3 H), 4.10 (s, 2 H), 6.83 (dd, *J* = 8.7, 2.7 Hz, 1 H), 7.04 (d, *J* = 2.7 Hz, 1 H), 7.32 (d, *J* = 8.7 Hz, 1 H), 7.33 (br s, 1 H).

Anal. Calcd for $C_{12}H_{14}N_2OS$: C, 61.51; H, 6.02; N, 11.96. Found: C, 61.57; H, 6.11; N, 11.86.

2-Methylsulfanyl-3-phenyl-3*H*-4,5-dihydro-1,3-benzodiazepine-4-thione (8a); Typical Procedure
A mixture of **5a** (0.11 g, 0.42 mmol), sulfur (16 mg, 0.50 mmol), and selenium (1.0 mg, 13 μmol) in THF (3 mL) was stirred at reflux temperature for 10 min. After cooling to r.t., NaH (60% in oil; 20 mg, 0.50 mmol) was added and the mixture was stirred for 30 min at the same temperature. MeI (72 mg, 0.50 mmol) was added using a microsyringe and the stirring was continued for an additional 20 min before sat. aq NH_4Cl (10 mL) was added. During the reaction, the progress of each step was monitored by TLC (silica gel) analyses. The organic materials were extracted with Et_2O (3 × 10 mL), and the combined extracts were washed with brine (15 mL), dried (Na_2SO_4), and concentrated by evaporation. The residue was purified by column chromatography on silica gel to afford the crude product, which was recrystallized to give pure **8a** as yellow crystals; yield: 87 mg (69%); R_f = 0.40 (CH_2Cl_2–hexane, 1:1); mp 195–196 °C (hexane–CH_2Cl_2).

IR (KBr): 1605, 1582, 1144 cm^{-1}.

^1H NMR (500 MHz): δ = 2.45 (s, 3 H), 4.21 (br s, 2 H), 7.17 (s, 2 H), 7.24–7.30 (m, 2 H), 7.38-7.45 (m, 5 H).

^{13}C NMR: δ = 16.05, 51.35, 124.00, 126.89, 127.21, 128.12 (2 C), 128.80, 129.25, 129.41, 142.04, 143.31, 153.98, 203.77.

MS: *m*/*z* (%) = 298 (79, $[M^+]$), 251 (100).

Anal. Calcd for $C_{16}H_{14}N_2S_2$: C, 64.39; H, 4.73; N, 9.39. Found: C, 64.30; H, 4.78; N, 9.58.

2-Ethylsulfanyl-3-phenyl-3*H*-4,5-dihydro-1,3-benzodiazepine-4-thione (8b)
Yellow crystal; R_f = 0.65 (THF–hexane, 1:4); mp 185–188 °C (hexane–THF).

IR (KBr): 1605, 1578, 1142 cm^{-1}.

^{1}H NMR (500 MHz): δ = 1.31 (t, *J* = 7.3 Hz, 3 H), 3.04 (q, *J* = 7.3 Hz, 2 H), 4.20 (br s, 2 H), 7.16 (s, 2H), 7.24–7.31 (m, 3 H), 7.38–7.45 (m, 4 H).

^{13}C NMR: δ = 13.56, 27.30, 51.32, 123.89, 126.94, 127.14, 128.09, 128.56, 128.74, 129.19, 129.35, 141.95, 143.32, 153.20, 203.68.

MS: *m*/*z* (%) = 312 (79, [M$^+$]), 283 (100).

Anal. Calcd for $C_{17}H_{16}N_2S_2$: C, 65.35; H, 5.16; N, 8.97. Found: C, 65.35; H, 5.15; N, 8.95.

3-Phenyl-2-phenylmethylsulfanyl-3*H*-4,5-dihydro-1,3-benzodiazepine-4-thione (8c)
Yellow oil; R_f = 0.60 (THF–hexane, 1:3).

IR (neat): 1607, 1582, 1144 cm^{-1}.

^{1}H NMR (500 MHz): δ = 4.01 (br s, 2 H), 4.27 (s, 2 H), 7.13 (s, 2 H), 7.24–7.32 (m, 7 H), 7.38–7.41 (m, 5 H).

^{13}C NMR: δ = 37.53, 51.32, 123.94, 126.97, 127.31, 127.42, 128.11, 128.46, 128.55, 128.79, 129.12, 129.28, 129.37, 136.35, 141.69, 143.19, 152.65, 203.67.

MS: *m*/*z* (%) = 374 (62, [M$^+$]), 283 (100).

Anal. Calcd for $C_{22}H_{18}N_2S_2$: C, 70.56; H, 4.84; N, 7.48. Found: C, 70.59; H, 4.80; N, 7.47.

3-(2-Chlorophenyl)-8-methyl-2-methylsulfanyl-3*H*-4,5-dihydro-1,3-benzodiazepine-4-thione (8d)
Pale-yellow solid; R_f = 0.32 (Et_2O–hexane, 1:20); 48–50 °C (hexane).

IR (KBr): 1620, 1593, 1146 cm^{-1}.

^{1}H NMR (500 MHz): δ = 2.39 (s, 3 H), 2.46 (s, 3 H), 4.21 (br s, 2 H), 7.08 (d, *J* = 7.8 Hz, 1 H), 7.09 (s, 1 H), 7.17 (d, *J* = 7.8 Hz, 1 H), 7.32–7.39 (m, 3 H), 7.45 (d, *J* = 8.2 Hz, 1 H).

^{13}C NMR: δ = 16.00, 21.17, 50.62, 124.31, 126.72, 127.32, 127.35, 127.71, 128.19, 130.49, 130.57, 138.07, 138.48, 138.77, 153.47, 160.42, 198.75.

MS: *m*/*z* (%) = 346 (82, [M$^+$]), 309 (100).

Anal. Calcd for $C_{17}H_{15}N_2S_2$: C, 58.86; H, 4.36; N, 8.08. Found: C, 58.75; H, 4.52; N, 7.91.

3-Ethyl-7-methoxy-2-methylsulfanyl-3*H*-4,5-dihydro-1,3-benzodiazepine-4-thione (8e)
Pale-yellow needles; R_f = 0.60 (THF–hexane, 1:4); mp 85–88 °C (hexane).

IR (KBr): 1614, 1593, 1121 cm^{-1}.

^{1}H NMR (500 MHz): δ = 1.20 (t, *J* = 6.9 Hz, 3 H), 2.55 (s, 3 H), 3.63–3.65 (m, 1 H), 3.81 (s, 3 H), 4.10–4.15 (m, 2 H), 4.47–4.53 (m, 1 H), 6.76 (d, *J* = 2.7 Hz, 1 H), 6.88 (dd, *J* = 8.7, 2.7 Hz, 1 H), 7.11 (d, *J* = 8.7 Hz, 1 H).

^{13}C NMR: δ = 12.16, 15.12, 48.38, 51.31, 55.55, 111.62, 115.12, 124.87, 127.74, 136.98, 153.26, 158.83, 200.25.

MS: *m*/*z* (%) = 280 (80, [M$^+$]), 243 (100).

Anal. Calcd for $C_{13}H_{16}N_2OS_2$: C, 55.68; H, 5.75; N, 9.99. Found: C, 55.42; H, 5.93; N, 10.15.

2-Allylsulfanyl-3-ethyl-7-methoxy-3*H*-4,5-dihydro-1,3-benzodiazepine-4-thione (8f)
Pale-yellow solid; R_f = 0.46 (THF–hexane, 1:9); mp 57–59 °C (hexane–Et_2O).

IR (KBr): 1611, 1578, 1153 cm^{-1}.

^{1}H NMR (500 MHz): δ = 1.18 (t, *J* = 7.3 Hz, 3 H), 3.62–3.75 (m, 2 H), 3.81 (s, 3 H), 3.84–3.88 (m, 1 H), 4.10–4.13 (m, 2 H), 4.47–4.54 (m, 1 H), 5.19 (d, *J* = 10.1 Hz, 1 H), 5.36 (dd, *J* = 16.9, 1.4 Hz, 1 H), 5.94–6.02 (m, 1 H), 6.76 (d, *J* = 2.7 Hz, 1 H), 6.88 (dd, *J* = 8.7, 2.7 Hz, 1 H), 7.10 (d, *J* = 8.7 Hz, 1 H).

^{13}C NMR: δ = 12.19, 34.92, 48.24, 51.28, 55.56, 111.61, 115.14, 118.72, 124.84, 127.78, 132.44, 136.87, 151.66, 158.92, 200.24.

MS: *m*/*z* (%) = 306 (32, [M$^+$]), 265 (100).

Anal. Calcd for $C_{15}H_{18}N_2OS_2$: C, 58.79; H, 5.92; N, 9.14. Found: C, 58.73; H, 6.02; N, 9.11.

2-Cyanomethylsulfanyl-3-ethyl-7-methoxy-3*H*-4,5-dihydro-1,3-benzodiazepine-4-thione (8g)
Pale-yellow needles; R_f = 0.50 (THF–hexane, 1:3); mp 140–141 °C (hexane–THF).

IR (KBr): 2245, 1614, 1593, 1123 cm^{-1}.

^{1}H NMR (500 MHz): δ = 1.22 (t, *J* = 6.9 Hz, 3 H), 3.65 (br s, 1 H), 3.82 (s, 5 H), 4.12–4.18 (m, 2 H), 4.52 (br s, 1 H), 6.76 (d, *J* = 2.7 Hz, 1 H), 6.91 (dd, *J* = 8.7, 2.7 Hz, 1 H), 7.21 (d, *J* = 8.7 Hz, 1 H).

^{13}C NMR: δ = 12.28, 17.87, 48.18, 51.37, 55.60, 111.72, 115.29, 115.78, 125.33, 127.56, 136.11, 147.99, 159.66, 200.65.

MS: *m*/*z* (%) = 305 (75, [M$^+$]), 265 (100).

Anal. Calcd for $C_{14}H_{15}N_3OS_2$: C, 55.06; H, 4.95; N, 13.76. Found: C, 55.04; H, 4.85; N, 13.75.

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