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A New Approach to the Synthesis of 1-Arylbenzimidazole-2-thiones from Nitroarenes and Anilines through Halogen-Free Substitution of Hydrogen via Iminophosphorane Intermediates

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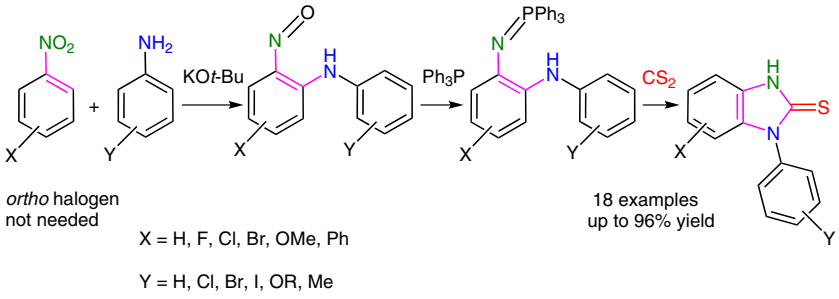

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Abstract 2-(Arylamino)phenyliminophosphoranes, formed directly from 2-nitrosodiarylamines, undergo a high-yielding cyclocondensation with CS_2, providing a variety of 1-arylbenzimidazole-2-thiones. The reaction concludes a new synthetic route leading to the title compounds from simple nitroarenes and arylamines. The protocol is superior to common methods that use *N*-arylarylenediamines because it omits the S_NAr substitution of halogen atoms in *ortho*-halonitroarenes, as well as reduction processes required for the synthesis of the intermediate diamines.

Key words annulation, nitrogen heterocycles, cyclization, nitroso compounds, fused-ring systems

Among the wide range of biologically active and pharmacologically important compounds based on a benzimidazole core, a significant place is taken by derivatives of 2-mercaptobenzimidazole, together with its 2-sufinyl analogues.[1] These compounds are known to possess a broad spectrum of activities and clinical applications. Antiviral,[2,3] antibacterial,[4] and antiulcer[5] activities are probably the most recognized properties.

Representative examples of pharmacologically approved structures include omeprazole, the most prominent proton pump inhibitor, and triclabendazole, an anthelmintic drug (Figure 1). S-Substituted 2-mercaptobenzimidazoles appear to be structures of interest in the search for compounds of potential analgesic,[6] antifugal,[4a–c] anticonvulsant,[6] antiprotozoal,[7] and noncataleptic[8] activity, among others.[9] It is worth mentioning that 2-mercaptobenzimidazoles are also convenient intermediates in the synthesis of a variety of biologically important 2-aminobenzimidazoles.[10]

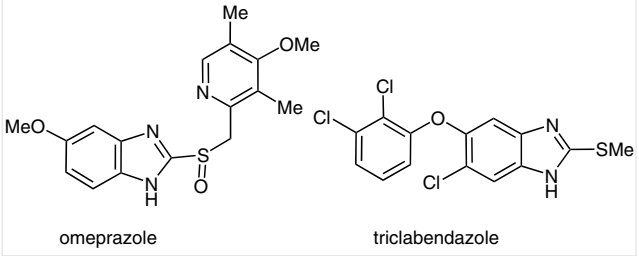
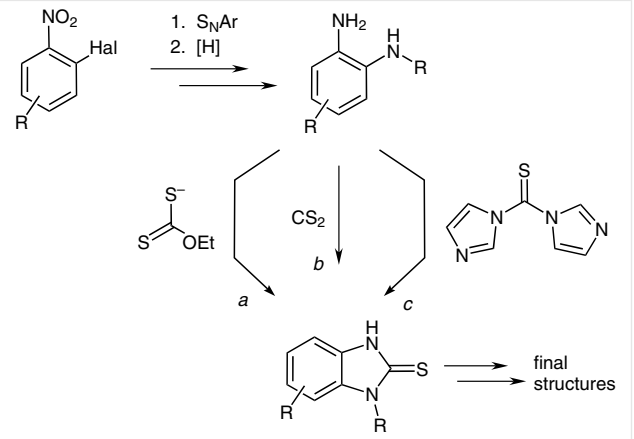


Figure 1 Representative drugs containing a 2-thio-substituted benzimidazole scaffold

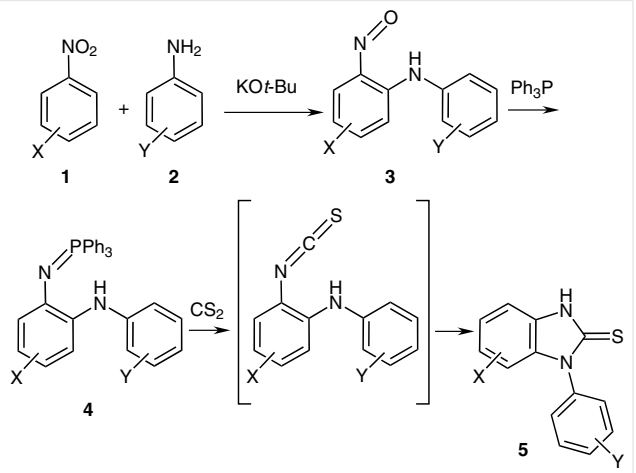
The majority of the examined 2-mercaptobenzimidazoles are those functionalized on the sulfur atom, often substituted at the fused benzene ring, but are generally unsubstituted at the imidazole nitrogen atoms. N-Alkylated or functionalized derivatives are less common;[1f,4d,7b,9a–d,11] nevertheless, in the past decade, noteworthy attention has focused on the synthesis of 1-*N*-aryl derivatives and on their considerable activities.[2a–c,3,9h,12–15]

The general scheme for the synthesis of the target compound involves the preparation of suitably substituted *o*-phenylenediamine and its cyclocondensation to form the corresponding benzimidazole-2-thione derivative, which is a fundamental starting material for further functionalization (Scheme 1).

There are several variants of the cyclocondensation. Probably the oldest and most common is a simple reaction of arylenediamines with carbon disulphide in the presence of KOH.[4b,7b,8,9a,c,i] Its modification employs potassium *O*-ethyl dithiocarbonate as a convenient equivalent of the previous reagent system,[10,16] thus avoiding the use of any hazardous compound. The last approach, which is used frequently nowadays, utilizes thiocarbonyldiimidazole (TCD), which is a simple, safe but relatively expensive reagent.[2a,3,12]



Scheme 1 Common routes for the synthesis of benzimidazole-2-thiones



Scheme 2 A new approach for the synthesis of 1-arylbenzimidazole-2-thiones

Both TDC and thiophosgene have been used to construct combinatorial libraries of 2-alkylthiobenzimidazoles.[11] Condensation of arylenediamines with ammonium thiocyanate has also been described.[17] A rather exceptional sequence started from *o*-haloanilines and involved intramolecular copper-catalyzed cyclization of *N*-arylthiourea derivatives.[18]

The starting *o*-phenylenediamines, if not commercially available, are usually synthesized from appropriate *o*-halogenonitrobenzenes through nucleophilic substitution of the *ortho* halogen atom, principally fluorine, with amines, followed by reduction of the nitro group. This sequence has, however, some drawbacks. It requires *ortho*-halogenated starting materials and these halogens are wasted in the subsequent process. The reduction requires the use of metal reductants or catalysts, thus, the method becomes both relatively expensive and not environmentally friendly. Moreover, *o*-phenylenediamines are rather unstable, air-sensitive compounds, which are difficult to purify. As a result, they are usually used immediately after their preparation, which may be impractical in certain cases.

Here, we present the use of 2-(arylamino)phenyliminophosphoranes as simple and stable equivalents of 2-arylarylenediamines in the synthesis of the title compounds (Scheme 2). Their use changes the entire reaction sequence, starting from nitroarenes, which becomes much more convenient and environmentally acceptable.

As we showed previously,[19] nitroarenes **1** and anilines **2** react in the presence of a strong base to form 2-nitrosodiarylamines **3**, which, in turn, readily condense with triphenylphosphane to deliver iminophosphoranes **4**.[20] The latter compounds appeared to be expedient starting materials for the synthesis of 2-aminobenzimidazoles[20] and benzotriazoles.[21] As an extension of previous work, this report presents a novel route to 1-arylbenzimidazole-2-thiones,[22] employing intermediate formation of isothiocyanates **4**.[23] Given that the first step of the reaction sequence constitutes the reductive version of a nucleophilic substitution of hydrogen, this approach does not require the presence of halogen atoms in the *ortho*-position of the nitroarene, which is indispensable in common S_NAr reactions, so it may be regarded as a halogen-free, thus more environment friendly, method.

In preliminary experiments investigating the crucial annulation step, 2-(arylamino)phenyliminophosphorane **4a** (X = OMe; Y = 4-Br) was subjected to the reaction with a five-fold molar excess of CS_2 in MeCN at room temperature, and benzimidazole-2-thione **5a** was isolated in 60% yield. To optimize the reaction conditions, other solvents were also examined (Table 1). The reaction appeared to be sensitive to the solvent used; the yield of product varied from

Table 1 Solvent Dependence of the Cyclocondensation of **4a** with CS_2[a]

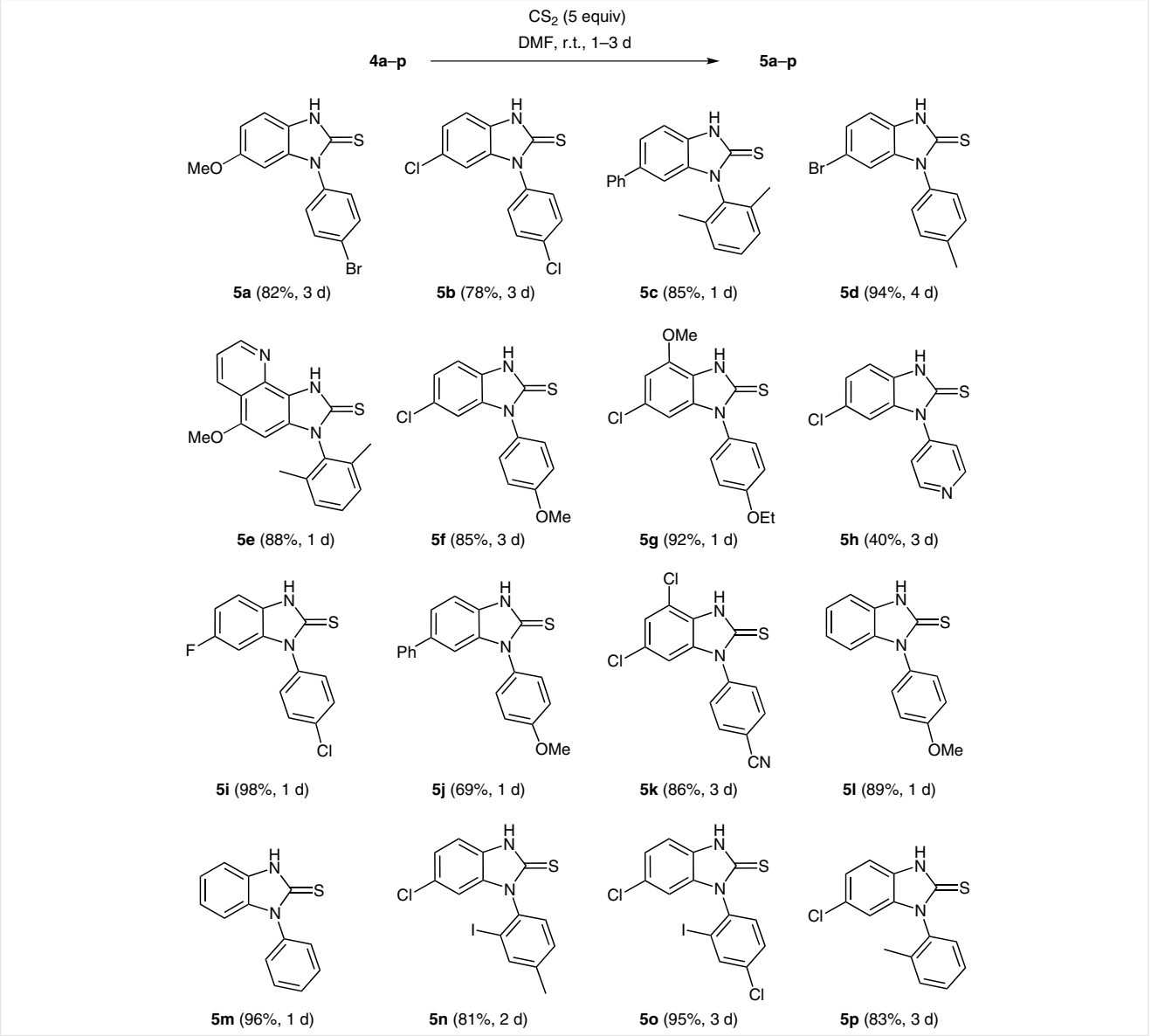
Entry	Solvent	Time (days)	Yield (%)[b]
1	MeCN	6	60
2	CH_2Cl_2	3	61
3	toluene	3	70
4	DMF	3	82
5	THF	3	71
6	EtOAc	1	76
7	Et_2O	14	54
8	MeOH	9	58
9	DMA	2	79
10	HMPA	2	94

[a] Reaction conditions: CS_2 (5 equiv), r.t., MeCN.
[b] Isolated yield.

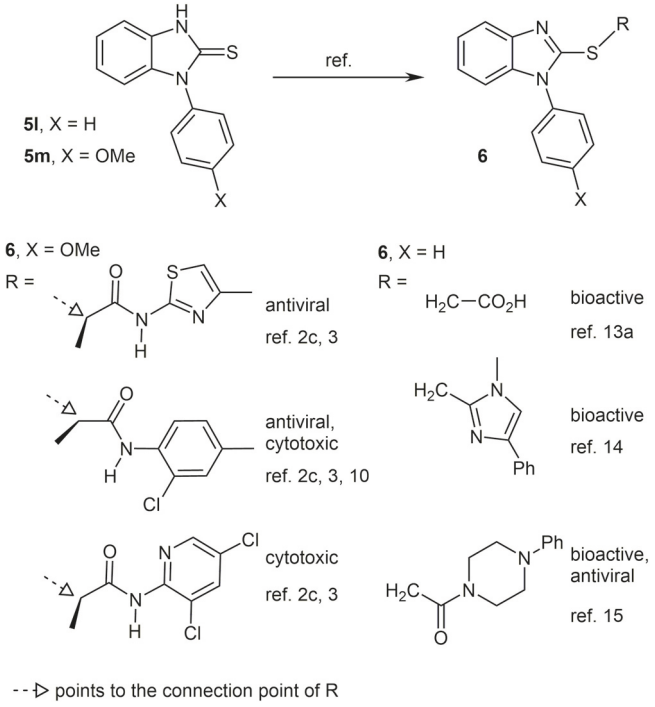
54% in Et_2O to 94% in hexamethylphosphoramide (HMPA). The time required to reach completion was also dependent on the nature of the solvent.

The best solvent regarding both these parameters was HMPA. However, because we wanted the protocol to be suitable for large-scale preparation, and HMPA is relatively hazardous, we chose DMF as the solvent for further investigations. A number of 1-arylbenzimidazole-2-thiones were synthesized under these reaction conditions (Scheme 3).

Several compounds **5** have been used as starting materials in the synthesis of interesting, biologically active targets (Scheme 4).[2,3,10,13–15] In 2013, the synthesis of a series of 1-arylbenzimidazole-2-thiones, with more complex 1-aryl moieties, was described, and some tests of antiviral and cytotoxic activities of their derivatives were reported in patents.[2a,c] Initial steps of those syntheses involved the preparation of the appropriate arylamine, which was then subjected to reaction with 2-fluoronitrobenzene followed by reduction of the formed 2-nitrodiarylamine, and condensation of the resultant *o*-arylenediamine with thiocarbonyldiimidazole (Route *c* in Scheme 1). To demonstrate the capability of the present method, we synthesized a pair of such benzimidazole-2-thiones starting from halogen-free nitrobenzene.



Scheme 3 Cyclocondensation of **4a–p** with CS_2, and synthesis of 1-arylbenzimidazole-2-thiones **5a–p**. Yields and reaction times (days) are indicated in parentheses.



Scheme 4 Examples of 1-aryl-2-mercaptobenzimidazole derivatives that exhibit recognized biological activity

The synthesis of **5q** was particularly appealing because the S_NAr substitution of fluorine in 2-fluoronitrobenzene with the appropriate arylamine was only moderately efficient (43% yield) and a product of the reduction of the *o*-nitroarylamine was unstable.[2a] We tried to overcome the problem by using our procedure, which omits formation of both *o*-nitroarylamines and *o*-arylenediamines as intermediates.

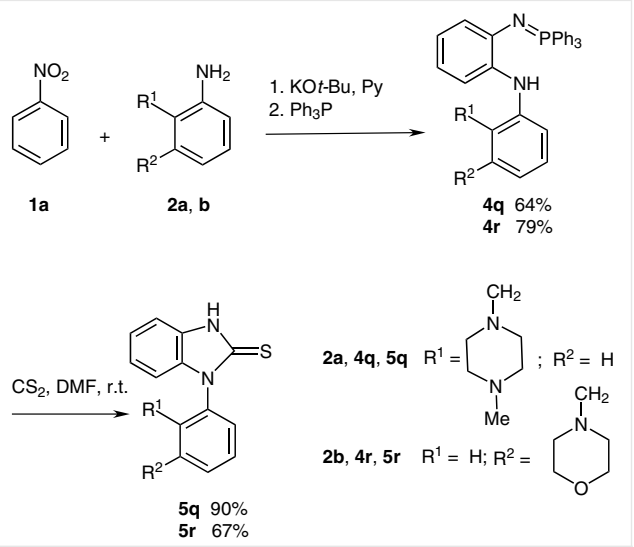
Reaction of nitrobenzene **1a** with triamine **2a** (prepared according to the procedure described by Moore et al.[2a]) in a mixture of THF and DMF with *t*-BuOK at –78 °C furnished **3a** in barely 27% yield as an impure product. The next steps, however, worked well, yielding **4q** and **5q** in 75 and 90% yield, respectively.

To improve the formation of **3a** it was necessary to overcome the problem of the solubility of **2a**, which did not dissolve in pure THF. Thus, whereas the reaction of **1a** and **2a** was performed in THF, a small amount of DMF was added as a solution of **2a**. It is known, that selective *ortho*-substitution in nitroarenes requires solvents of rather low polarity, and dipolar aprotic solvents are not suitable for the reactions of *para*-unsubstituted nitrobenzene derivatives.[19,24]

After optimization, pyridine, a solvent of relatively low polarity that readily dissolved amine **2a**, was chosen as a cosolvent in combination with THF. Upon completion of the reaction, crude nitrosoaniline **3a** was converted in situ into iminophosphorane **4q** by quenching the reaction mixture with a roughly stoichiometric amount of acetic acid (AcOH), and subsequent addition of PPh_3 (2.5 equiv). The reaction, which was carried out at room temperature for 24 hours, gave **4q** in 64% yield for two steps. Given that separation of **4q** from Ph_3PO was difficult and laborious, a more effective procedure was then applied. Crude **4q** was subjected to rough and quick column chromatography resulting in partial separation from Ph_3PO. The impure product was dissolved in DMF and stirred with CS_2 (5 equiv) for three days to furnish pure **5q** after chromatography in total 50% yield for three steps, starting from nitrobenzene **1a** (Scheme 5). The result was a remarkable improvement over the 30% yield of this compound reported in the synthesis starting from 2-fluoronitrobenzene.[2a]

The procedure was then applied to 3-morpholinylmethylaniline **2b**[25] (Scheme 5), which furnished **5r** in 67% yield over three steps, vs. 53% yield reported for the synthesis of this compound starting from 2-fluoronitrobenzene.[2a]

In conclusion, we have developed a useful, alternative route for the synthesis of 1-arylbenzimidazole-2-thiones that is superior to previous methods not only because of its mild and simple conditions, but also because the approach replaces the S_NAr substitution of halogens with hydrogen substitution; thus, the approach delivers a halogen-free protocol for the synthesis. Moreover, it allows the target molecules to be synthesized from simpler, less expensive nitroarenes and enables the synthesis to be performed on a wider range of nitroarenes because a number of *ortho*-halo analogues are not easy to synthesize. On the other hand, *para*-halogens, including fluorine, can be preserved



Scheme 5 Synthesis of 1-arylbenzimidazole-2-thiones **5q** and **5r**

throughout the whole sequence. The method seems to be especially beneficial in cases when arylenediamine intermediates, required in the classical synthetic approach for the thiocarbonylation process, are unstable.

Melting points of solid compounds are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded with a Varian Mercury 400 MHz and a Varian VNMRS 600 MHz instruments at 298 K. Chemical shifts are reported in ppm referred to TMS (^{1}H NMR at 400 and 600 MHz) or to the solvent used (^{13}C NMR at 100 and 150 MHz, respectively), coupling constants are given in Hertz. Mass spectra were obtained with a GCT Premier spectrometer (EI, 70 eV) or with an API 365i apparatus (ESI in MeOH). IR spectra were recorded with a FT/IR Jasco 6200 spectrometer in KBr. Silica gel Merck 60 (230–400 mesh) was used for column chromatography. THF was distilled from sodium/benzophenone ketyl prior to use. DMF was dried over CaH_2, distilled, and stored over molecular sieves. Common reagents and materials were purchased from commercial sources and used as received. Preparation and characterization of new 2-(arylamino)phenyliminophosphoranes **4** and starting *N*-aryl-2-nitrosoanilines **3** are described in the Supporting Information.

Benzimidazole-2-thiones 5a–q; General Procedure

The appropriate iminophosphorane **4** (0.5 mmol) was dissolved in anhydrous DMF (5 mL), and CS_2 (3 mmol, 0.18 mL) was added in one portion. The reaction flask was stoppered and the mixture was stirred at r.t. Upon completion of the reaction (1–3 days, reaction monitored by TLC), the mixture was poured into H_2O and extracted with EtOAc. The organic phase was dried over Na_2SO_4 and, after evaporation, the residue was purified by silica gel column chromatography (hexane–EtOAc, 9:1 to 2:1). An analytically pure sample of the product was obtained by recrystallization from chloroform–hexane.

1-(4-Bromophenyl)-6-methoxy-2,3-dihydro-1*H*-1,3-benzodiazole-2-thione (5a)

Yield: 137 mg (82%); white solid; mp 251–254 °C.

IR (KBr): 3060, 1500, 1490, 1351, 1227 cm^{-1}.

^{1}H NMR (600 MHz, acetone-d_6): δ = 3.76 (s, 3 H), 6.59 (d, *J* = 2.4 Hz, 1 H), 6.85–6.88 (dd, *J* = 8.7, 2.4 Hz, 1 H), 7.24 (d, *J* = 8.7 Hz, 1 H), 7.55–7.58 (m, 2 H), 7.79–7.81 (m, 2 H), NH signal not observed.

^{13}C NMR (150 MHz, acetone-d_6): δ = 56.2, 95.8, 111.1, 111.6, 122.7, 126.0, 131.0, 133.4, 135.6, 136.1, 157.7, 171.1.

MS (EI): *m*/*z* (%) = 336 (100), 335 (62), 334 (97), 321 (17), 319 (17), 239 (17), 154 (18).

HRMS (EI): *m*/*z* calcd for $C_{14}H_{11}N_2OS^{79}Br$: 333.9775; found: 333.9781.

6-Chloro-1-(4-chlorophenyl)-2,3-dihydro-1*H*-1,3-benzodiazole-2-thione (5b)[26]

Yield: 115 mg (78%); white solid; mp 281–283 °C.

IR (KBr): 3128, 3069, 1605, 1498, 1335, 1212 cm^{-1}.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 6.96 (d, *J* = 1.3 Hz, 1 H), 7.24–7.28 (m, 2 H), 7.58–7.60 (m, 2 H), 7.66–7.69 (m, 2 H), 13.23 (s, 1 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 109.2, 110.9, 123.4, 127.2, 129.6, 129.9, 130.0, 133.5, 133.7, 134.4, 170.1.

MS (EI): *m*/*z* (%) = 296 (62), 295 (84), 294 (91), 293 (100), 258 (21), 224 (11), 156 (13), 124 (12), 111 (26).

HRMS (EI): *m*/*z* calcd for $C_{13}H_8N_2S^{35}Cl_2$: 293.9785; found: 293.9791.

1-(2,6-Dimethylphenyl)-6-phenyl-2,3-dihydro-1*H*-1,3-benzodiazole-2-thione (5c)

Yield 140 mg (85%); white solid; mp 233–236 °C.

IR (KBr): 3043, 1601. 1486, 1448, 1429, 1342, 1221, 760, 698 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.94 (s, 6 H), 6.71 (br. s, 1 H), 7.25–7.44 (m, 7 H), 7.46–7.58 (m, 3 H), 13.12 (br. s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 17.5, 106.5, 110.4, 122.5, 126.8, 127.2, 128.6, 128.9, 129.3, 131.0, 132.8, 132.3, 135.5, 136.5, 139.9, 168.8.

MS (EI): *m*/*z* (%) = 330 (50), 298 (25), 297 (100), 282 (14).

HRMS (EI): *m*/*z* calcd for $C_{21}H_{18}N_2S$: 330.1191; found: 330.1187.

6-Bromo-1-(4-methylphenyl)-2,3-dihydro-1*H*-1,3-benzodiazole-2-thione (5d)

Yield: 150 mg (94%); white solid; mp 257–260 °C.

IR (KBr): 3127, 3069, 1515, 1489, 1337, 811, 795, 605 cm^{-1}.

^{1}H NMR (600 MHz, acetone-d_6): δ = 2.46 (s, 3 H), 7.04–7.05 (d, *J* = 1.8 Hz, 1 H), 7.28 (d, *J* = 8.4 Hz, 1 H), 7.37–7.40 (dd, *J* = 8.4, 1.8 Hz, 1 H), 7.44 (s, 4 H), one signal not observed.

^{13}C NMR (150 MHz, acetone-d_6): δ = 21.2, 111.8, 113.0, 115.8, 126.8., 128.6, 130.9, 131.3, 133.7, 136.6, 139.8, 172.3.

MS (EI): *m*/*z* (%) = 320 (89), 319 (100), 318 (87), 317 (84), 238 (24).

HRMS (EI): *m*/*z* calcd for $C_{14}H_{11}N_2S^{79}Br$: 317.9826; found: 317.9871.

3-(2,6-Dimethylphenyl)-5-methoxy-1*H*,2*H*,3*H*-imidazo[4,5-*h*]quinoline-2-thione (5e)

Yield: 148 mg (88%); orange crystals; mp > 290 °C.

IR (KBr): 3026, 1637, 1592, 1526, 1489, 1359, 1242, 1140, 790, 769, 604 cm^{-1}.

^{1}H NMR (600 MHz, CF_3CO_2D): δ = 2.03 (s, 6 H), 4.02 (s, 3 H), 6.77 (s, 1 H), 7.36–7.39 (m, 2 H), 7.50–7.54 (m, 1 H), 8.06 (s, 1 H), 9.14–9.17 (m, 1 H), 9.59 (d, *J* = 8.3 Hz, 1 H), 11.51 (s, 1 H).

^{13}C NMR (150 MHz, CF_3CO_2D): δ = 18.1, 58.8, 94.6, 122.8, 123.9, 127.9, 131.4, 132.1, 134.6, 138.8, 140.9, 146.3, 147.2, 158.5, two signals not observed.

MS (EI): *m*/*z* (%) = 335 (77), 303 (25), 302 (100), 287 (27), 272 (10).

HRMS (EI): *m*/*z* calcd for $C_{19}H_{17}N_3OS$: 335.1092; found: 335.1101.

6-Chloro-1-(4-methoxyphenyl)-2,3-dihydro-1*H*-1,3-benzodiazole-2-thione (5f)[26]

Yield: 123 mg (85%); white solid; mp 253–255 °C.

IR (KBr): 3127, 3069, 2946, 1610, 1517, 1487, 1335, 1256, 1211, 1170, 801, 609 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.90 (s, 3 H), 6.93 (s, 1 H), 7.01–7.21 (m, 4 H), 7.35–7.47 (m, 2 H), 12.02 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.7, 110.4, 110.9, 115.2, 124.1, 127.3, 129.1, 129.3, 129.4, 135.3, 160.4, 170.2.

MS (EI): *m*/*z* (%) = 292 (38), 291 (42), 290 (100), 289 (65), 275 (23).

HRMS (EI): *m*/*z* calcd for $C_{14}H_{11}N_2OS^{35}Cl$: 290.0281; found: 290.0295.

6-Chloro-1-(4-ethoxyphenyl)-4-methoxy-2,3-dihydro-1*H*-1,3-benzodiazole-2-thione (5g)

Yield: 153 mg (92%); white solid; mp 257–260 °C.

IR (KBr): 3029, 2888, 1636, 1610, 1585, 1519, 1497, 1478, 1345, 1250, 1229, 1119, 896, 660 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.46 (t, *J* = 6.4 Hz, 3 H), 3.92 (s, 3 H), 4.11 (q, *J* = 6.4 Hz, 2 H), 6.55 (s, 1 H), 6.70 (s, 1 H), 7.03–7.10 (m, 2 H), 7.34–7.41 (m, 2 H), 11.04 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.9, 56.4, 64.0, 103.4, 106.5, 115.6, 119.3, 127.5, 129.0, 129.6, 135.9, 144.5, 159.6, 169.7.

MS (EI): *m*/*z* (%) = 336 (38), 335 (38), 334 (100), 333 (50), 307 (10), 305 (28).

HRMS (EI): *m*/*z* calcd for $C_{16}H_{15}N_2O_2S^{35}Cl$: 334.0543; found: 334.0552.

6-Chloro-1-(pyridin-4-yl)-2,3-dihydro-1*H*-1,3-benzodiazole-2-thione (5h)

Yield: 52 mg (40%); white solid; mp 274–277 °C.

IR (KBr): 3029, 2888, 1636, 1610, 1585, 1519, 1497, 1478, 1345, 1250, 1229, 1119, 896, 660 cm^{-1}.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 7.12 (d, *J* = 1.9 Hz, 1 H), 1.27 (d, *J* = 8.5 Hz, 1 H), 7.29–7.31 (dd, *J* = 8.9, 1.9 Hz, 1 H), 7.70–7.72 (m, 2 H), 8.83–8.85 (m, 2 H), 13.35 (s, 1 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 109.5, 111.1, 122.5, 123.8, 127.3, 130.2, 133.5, 142.3, 151.2, 169.6.

MS (EI): *m*/*z* (%) = 263 (37), 262 (51), 261 (100), 260 (95), 225 (12).

HRMS (EI): *m*/*z* calcd for $C_{12}H_8N_3S^{35}Cl$: 261.0127; found: 261.0135.

1-(4-Chlorophenyl)-6-fluoro-2,3-dihydro-1*H*-1,3-benzodiazole-2-thione (5i)

Yield: 136 mg (98%); white crystals; mp 258–261 °C.

IR (KBr): 3141, 3093, 1618, 1502, 1489, 1448, 1349, 1217, 1092, 799, 600 cm^{-1}.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 6.82–6.84 (dd, *J* = 8.6, 2.2 Hz, 1 H), 7.06–7.10 (m, 1 H), 7.23–7.25 (d, *J* = 4.8 Hz, 1 H), 7.57–7.60 (m, 2 H), 7.66–7.68 (m, 2 H), 13.16 (s, 1 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 97.2 (d, J_{C-F} = 29 Hz), 110.4 (d, J_{C-F} = 20 Hz), 110.6 (d, J_{C-F} = 3 Hz), 127.6, 129.5, 129.9, 133.4, 133.8, 134.0 (d, J_{C-F} = 13 Hz), 158.7 (d, J_{C-F} = 237 Hz), 170.2.

MS (EI): *m*/*z* (%) = 280 (34), 279 (50), 278 (92), 277 (100), 242 (15).

HRMS (EI): *m*/*z* calcd for $C_{13}H_8N_2FS^{35}Cl$: 278.0081; found: 278.0078.

1-(4-Methoxyphenyl)-6-phenyl-2,3-dihydro-1*H*-1,3-benzodiazole-2-thione (5j)

Yield: 120 mg (72%); white crystals; mp 221–224 °C.

IR (KBr): 3159, 3056, 1611, 1585, 1519, 1478, 1447, 1351, 1302, 1255, 1026, 826, 757 cm^{-1}.

^{1}H NMR (600 MHz, acetone-d_6): δ = 3.90 (s, 3 H), 7.12–7.17 (m, 3 H), 7.31–7.34 (m, 1 H), 7.40–7.43 (m, 3 H), 7.51–7.55 (m, 3 H), 7.57–7.59 (m, 2 H), 11.98 (s, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 55.6, 108.5, 110.4, 115.0, 123.2, 127.2, 127.3, 127.7, 128.8, 129.1, 130.2, 135.1, 137.0, 140.7, 160.0, 169.4.

^{1}H-^{15}N NMR (600 MHz, acetone-d_6): δ = –230.37 (d, *J* = 100 Hz, NH), –216.31.

MS (EI): *m*/*z* (%) = 332 (100), 331 (49), 317 (18).

HRMS (EI): *m*/*z* calcd for $C_{20}H_{16}N_2OS$: 332.0983; found: 332.0989.

4-(4,6-Dichloro-2-sulfanylidene-2,3-dihydro-1*H*-1,3-benzodiazol-1-yl)benzonitrile (5k)

Yield: 138 mg (86%); white solid; mp >280 °C.

IR (KBr): 3106, 3047, 2898, 2233, 1603, 1508, 1488, 1329, 1257, 1177, 840 cm^{-1}.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 6.99 (d, *J* = 1.7 Hz, 1 H), 7.46 (d, *J* = 1.7 Hz, 1 H), 7.80–7.82 (m, 2 H), 8.10–8.12 (m, 2 H), 13.84 (s, 1 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 108.4, 111.9, 114.5, 118.2, 122.9, 127.6, 128.4, 129.4, 133.7, 135.0, 138.7, 170.9.

MS (EI): *m*/*z* (%) = 321 (60), 320 (84), 319 (89), 318 (100), 75 (11).

HRMS (EI): *m*/*z* calcd for $C_{14}H_7N_3S^{35}Cl_2$: 318.9738; found: 318.9736.

1-(4-Methoxyphenyl)-2,3-dihydro-1*H*-1,3-benzodiazole-2-thione (5l)[26]

Yield: 114 mg (89%); white crystals; mp 217–220 °C.

IR (KBr): 3134, 3090, 3054, 2985, 1615, 1586, 1515, 1451, 1383, 1360, 1313, 1249, 1217, 1161, 1034, 823, 732, 623, 565 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 3.89 (s, 3 H), 6.96 (d, *J* = 8.0 Hz, 1 H), 7.08–7.10 (m, 2 H), 7.16 (t, *J* = 7.7 Hz, 1 H), 7.23 (t, *J* = 7.7 Hz, 1 H), 7.34 (d, *J* = 8.0 Hz, 1 H), 7.45–7.47 (m, 2 H), one signal not observed.

^{13}C NMR (150 MHz, $CDCl_3$): δ = 55.6, 110.1, 110.4, 114.9, 123.3, 123.9, 127.6, 129.0, 130.7, 134.5, 160.0, one signal not observed.

MS (EI): *m*/*z* (%) = 256 (100), 255 (70), 241 (35).

HRMS (EI): *m*/*z* calcd for $C_{14}H_{12}N_2OS$: 256.0670; found: 256.0666.

6-Chloro-1-(2-iodo-4-methylphenyl)-2,3-dihydro-1*H*-1,3-benzodiazole-2-thione (5n)

Yield: 162 mg (81%); white solid; mp 235–238 °C.

IR (KBr): 3129, 3024, 2944, 2910, 1608, 1592, 1497, 1471, 1434, 1369, 1335, 1243, 1213, 1195, 1048, 945, 839, 796, 609, 588 cm^{-1}.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 2.39 (s, 3 H), 6.64 (s, 1 H), 7.24–7.26 (m, 2 H), 7.35 (d, *J* = 8.0 Hz, 1 H), 7.40–7.45 (m, 1 H), 7.90–7.91 (m, 1 H), 13.14 (s, 1 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 20.2, 99.1, 109.1, 110.9, 123.2, 127.0, 130.0, 130.1, 130.4, 134.1, 134.8, 139.9, 141.5, 170.2.

MS (ESI): m/z = 400.9 $[M + H]^+$, 422.9 $[M + Na]^+$.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{14}H_{11}N_2S^{35}ClI$: 400.9376; found: 400.9372.

6-Chloro-1-(4-chloro-2-iodophenyl)-2,3-dihydro-1*H*-1,3-benzodiazole-2-thione (5o)

Yield: 200 mg (95%); orange solid; mp 255–257 °C.

IR (KBr): 3069, 3042, 2942, 1606, 1572, 1488, 1469, 1433, 1335, 1205, 1193, 1095, 807, 781, 722, 600 cm^{-1}.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 6.81 (s, 1 H), 7.25–7.27 (m, 2 H), 7.53 (d, J = 8.4 Hz, 1 H), 7.68–7.71 (dd, J = 8.4, 2.4 Hz, 1 H), 8.17 (d, J = 2.4 Hz, 1 H), 13.20 (s, 1 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 100.9, 109.4, 110.9, 123.4, 127.2, 129.8, 130.2, 131.9, 133.9, 134.9, 136.7, 138.8, 170.0.

MS (EI): m/z (%) = 422 (4), 420 (6), 293 (100), 292 (65), 260 (12), 259 (10), 258 (34).

HRMS (EI): m/z calcd for $C_{13}H_7N_2S^{35}Cl_2I$: 419.8752; found: 419.8878.

6-Chloro-1-(2-iodophenyl)-2,3-dihydro-1*H*-1,3-benzodiazole-2-thione (5p)

Yield: 114 mg (83%); white solid; mp 190–193 °C.

IR (KBr): 3286, 1605, 1583, 1500, 1478, 1422, 1373, 1332, 1197, 1184, 1119, 844, 800, 730, 634, 591 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.14 (s, 3 H), 6.72 (s, 1 H), 7.19–7.22 (m, 2 H), 7.28–7.32 (m, 1 H), 7.41–7.52 (m, 3 H), 12.16 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.0, 110.2, 111.0, 124.1, 127.7, 128.4, 129.4, 129.7, 130.4, 131.9, 133.6, 134.9, 169.8, one signal not observed.

MS (EI): m/z (%) = 276 (18), 275 (10), 274 (49), 259 (11), 243 (34), 242 (19), 241 (100), 206 (11), 205 (11).

HRMS (EI): m/z calcd for $C_{14}H_{11}N_2S^{35}Cl$: 274.0331; found: 274.0331.

1-{2-[(4-Methylpiperazin-1-yl)methyl]phenyl}-2,3-dihydro-1*H*-1,3-benzodiazole-2-thione (5q)[2a]

Yield: 152 mg (90%); white solid; mp 92–96 °C.

IR (KBr): 3052, 2934, 2802, 1498, 1454, 1357, 1309, 1265, 1216, 1010, 822, 740, 631 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.10–2.35 (m, 11 H), 3.30 (d, J = 16.0 Hz, 1 H), 3.60 (d, J = 12.0 Hz, 1 H), 6.69 (d, J = 8.0 Hz, 1 H), 7.07–7.11 (m, 1 H), 7.14–7.19 (m, 1 H), 7.20–7.24 (m, 1 H), 7.33–7.36 (m, 1 H), 7.45–7.53 (m, 2 H), 7.61–7.64 (m, 1 H), one signal not observed.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 45.6, 52.9, 54.7, 59.4, 109.9, 110.3, 122.8, 123.4, 128.6, 129.3, 129.9, 131.1, 131.2, 134.5, 135.2, 137.7, 169.0.

MS (EI): m/z (%) = 338 (19), 337 (10), 282 (23), 268 (32), 240 (18), 239 (100), 237 (20), 205 (40), 180 (25).

HRMS (EI): m/z calcd for $C_{19}H_{22}N_4S$: 338.1565; found: 338.1550.

1-[3-(Morpholin-4-ylmethyl)phenyl]-2,3-dihydro-1*H*-1,3-benzodiazole-2-thione (5r)[2a]

Iminophosphorane **4r** (3.3 mmol, 1800 mg) was dissolved in anhydrous DMF (10 mL), and CS_2 (16.5 mmol, 1.0 mL) was added in one portion. The reaction flask was stoppered and the mixture was stirred at r.t. for 3 days (reaction was monitored by TLC). Upon completion of the reaction, the mixture was poured into H_2O, extracted with EtOAc, and the organic phase was dried over Na_2SO_4. After evaporation, the residue was purified by silica gel column chromatography (hexane–EtOAc, 9:1 to 2:1).

Yield: 597 mg (67%); white solid; mp 137–140 °C.

IR (KBr): 3052, 2926, 2851, 2805, 1602, 1591, 1509, 1456, 1298, 1253, 1221, 1205, 1112, 734, 702 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.50–2.56 (m, 4 H), 3.61–3.65 (m, 2 H), 3.72–3.77 (m, 4 H), 6.95 (d, J = 8.0 Hz, 1 H), 7.12–7.17 (m, 1 H), 7.19–7.24 (m, 1 H), 7.25–7.30 (m, 1 H), 7.42–7.46 (m, 1 H), 7.47–7.50 (m, 1 H), 7.51–7.55 (m, 1 H), 7.56–7.59 (m, 1 H), 11.73 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 53.7, 62.9, 67.4, 110.1, 110.2, 123.2, 123.9, 126.5, 128.5, 129.6, 129.9, 130.9, 134.3, 135.4, 140.0, 169.2.

MS (EI): m/z (%) = 325 (9), 307 (14), 282 (12), 241 (19), 240 (100), 119 (13).

HRMS (EI): m/z calcd for $C_{18}H_{19}N_3SO$: 325.1249; found: 325.1241.

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Supporting Information

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