Rearrangement Reactions; 14:[1] Synthesis of Functionalized Thiazoles via Attack of Heteroatom Nucleophiles on Allenyl Isothiocyanates

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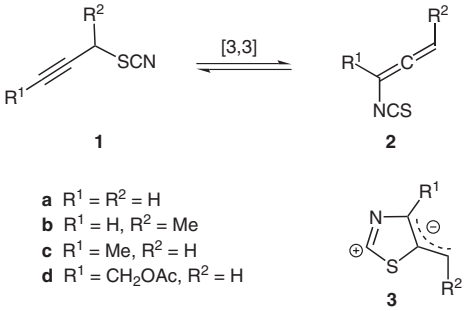
Dedicated to Professor Wolfgang Kirmse on the occasion of his 75th birthday

Abstract: Treatment of allenyl isothiocyanates with sulfur-, oxygen-, nitrogen- or hydride-containing nucleophiles such as propane-2-thiol, thiophenol, hydrogen sulfide, alcohols, phenol or aqueous NaOH, NH_3, primary or secondary aliphatic or aromatic amines, *N*,*N*,*N*′,*N*′-tetramethylguanidine or sodium cyanoborohydride resulted in ring closure to generate thiazoles bearing a functionality at position C-2 in most cases. Moreover, we report the first examples of aromatic thiazole-2-phosphonates prepared by the same strategy using dialkyl or diphenyl phosphites as nucleophiles.

Key words: allenes, isothiocyanates, addition reactions, ring closure, heterocycles



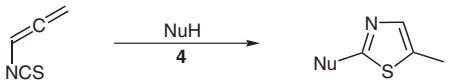
Scheme 1

Recently, we reported[2] that the well known[3] isomerization of allyl thiocyanate to allyl isothiocyanate can be transferred to propargyl thiocyanates **1** as an alternative starting material yielding allenyl isothiocyanates **2** (Scheme 1). However, in general this [3,3]-sigmatropic rearrangement **1** → **2** can be performed only by the technique of flash vacuum pyrolysis (FVP) successfully because neat (undiluted) cumulenes, such as **2**, tend to exothermic spontaneous polymerization even at room temperature. Whereas allenyl isothiocyanates like **2a** and **2b** can be obtained nearly quantitatively in hundred-gram batches per day, there are some limitations in other cases such as **2c** and **2d**. Flash vacuum pyrolysis of **1c** leads to equilibrium with **2c** (ratio **1c/2c** = 17:83) while rearrangement **1d** → **2d** is nearly irreversible. However, the yield of **2d** is limited to 73% since the precursor **1d** cannot be vaporized without decomposition.

We present now the reactions of the isothiocyanates **2** with sulfur-, phosphorus-, oxygen-, nitrogen- and hydride-containing nucleophiles leading to thiazole[4] derivatives. Thus, the chemistry of **2** illustrates that allenyl isothiocyanates act predominantly as synthetic equivalents of synthons **3**.

Thiazole **5b** was prepared (87% yield) by treating the allene **2a** at room temperature with sodium thiophenolate generated from **4b** and NaH (Table 1). On the other hand, the reaction of propane-2-thiol (**4a**) with the same allene **2a** at room temperature gave heterocycle **5a** (70% yield) without the need of any base.

Table 1 Transformation of **2a** to Thiazoles **5a–o** via Attack of Heteroatom Nucleophiles NuH **4**



2a **5a–o**

4	NuH	Yield of **5** (%)	Ref[a]
a	Me_2CHSH	70	
b	PhSH[b]	87	5
c	$(MeO)_2P(O)H$	83	
d	$(PhCH_2O)_2P(O)H$	88	
e	$(PhO)_2P(O)H$	90	
f	MeOH	69	6
g	Me_2CHOH	52	
h	PhOH[c]	68	
i	NH_3	59	7
j	$CH_3CH_2CH_2NH_2$	45	
k	$PhNH_2$	82	8
l	Ph_2NH	40	
m	$MeO_2CCH_2NH_2$	67	
n	*o*-$MeO_2CC_6H_4NH_2$	56	
o	$(Me_2N)_2C{=}NH$	95	

[a] References to compounds **5** prepared by other methods.
[b] Thiophenol in the presence of NaH.
[c] With addition of NaOH.

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Using dialkyl or diphenyl phosphites for nucleophilic addition to **2a** could give rise to C–P bond formation, but treating of the appropriate phosphites **4c–e** with allene **2a** did not lead to heterocyclic products. Repeating the same reaction, however, in the presence of K_2CO_3, which serves as a heterogeneous catalyst, gives newly substituted thiazoles **5c–e** in very good yields. Actually, these are the first examples of aromatic substituted thiazoles bearing a phosphorus atom of a phosphonate group directly bonded to the thiazole ring at C-2 position. Thus, the ^{13}C NMR spectra of heterocycles **5c–e** revealed the significant C(2)–P and C(4)–P couplings summarized in Table 2.

Table 2 Some C–P Coupling Constants of Compounds **5c–e**[a]

^{13}C NMR		Compound No.		
		5c	**5d**	**5e**
C-2	$^1J_{PC}$ (Hz)	245.8	247.6	256.6
C-4	$^3J_{PC}$ (Hz)	26.2	26.8	28.4
$-OCH_3$	$^2J_{PC}$ (Hz)	6.2	–	–
$-OCH_2Ph$	$^2J_{PC}$ (Hz)	–	5.6	–
Ph_i	$^3J_{PC}$ (Hz)	–	6.8	–
Ph_i	$^2J_{PC}$ (Hz)	–	–	7.4
Ph_o	$^3J_{PC}$ (Hz)	–	–	4.6
Ph_m	$^4J_{PC}$ (Hz)	–	–	1.1

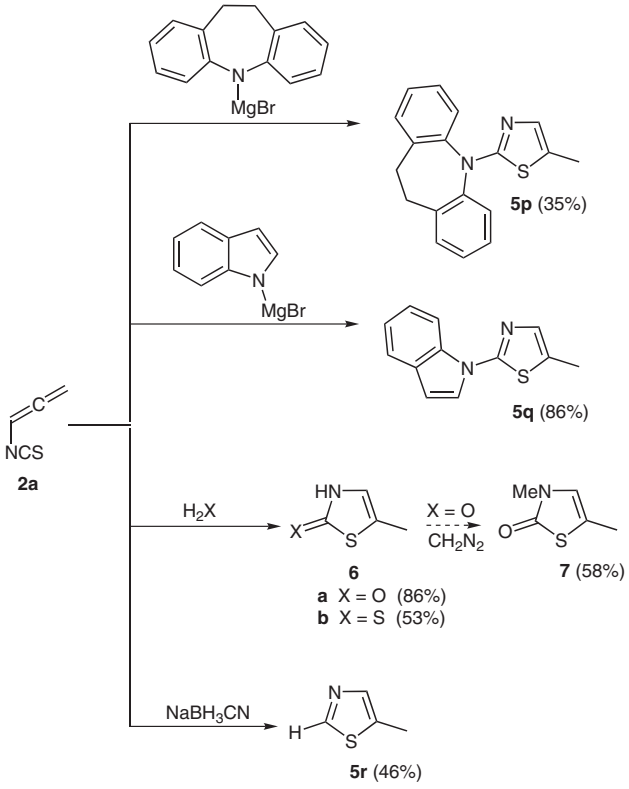
[a] No coupling was detected between the phosphorus atom and C-5 of the thiazole moiety.

Allene **2a** could be reacted with alcohols **4f** and **4g** as well as phenol (**4h**) to afford the substituted thiazoles **5f**, **5g**, **5h**, respectively, with moderate yields. In the case of **4h**, NaOH was used to facilitate the reaction pathway due to the well-known low nucleophilicity of phenol if compared to that of alcohols on the one hand and that of phenolate on the other hand.

Unlike phenols, amines and even NH_3 can be reacted with isothiocyanate **2a** in the absence of any base because of the superior nucleophilicity of these nitrogen compounds. Thus, treatment of allene **2a** with amines **4i–l**, **4m**,[9] **4n** furnished the thiazoles **5i–n** with moderate to very good yields. In some cases, the transformations are highly exothermic. Thus, dilution with an inert solvent and cooling of the reaction mixtures are necessary. The cumulene **2a** is extremely reactive if compared to other isothiocyanates. This is exemplified by the conversion of **2a** with diphenylamine (**4l**) leading to thiazole **5l** already at room temperature. Phenyl isothiocyanate is attacked by the weak nitrogen nucleophile **4l** only at 280 °C.[10]

In the case of guanidine **4o**, the resulting yield of the isolated heterocycle **5o** (95%) was excellent. Moreover, the C–N bond formation was achieved via the reaction of allene **2a** with dibenzoazepinylmagnesium bromide and indolylmagnesium bromide in THF to generate the newly substituted thiazoles **5p** (35%) and **5q** (86%), respectively (Scheme 2). It is important to mention that the isothiocyanate **2a** did not react with either dibenzoazepine or indole even after several days at room temperature. This can be attributed to the poor availability of the lone pair of amines bearing two aromatic substituents. In the case of indole, the lone pair at the nitrogen atom is involved within the aromaticity of the heterocyclic moiety causing a significantly decreased nucleophilicity.

The reaction of isothiocyanate **2a** with diluted aqueous NaOH or aqueous H_2S afforded the two heterocycles **6a**[6] and **6b**[11] with 86% and 53% yields, respectively. The structure of **6a** was determined not only by its spectroscopic data but also by treating with diazomethane[12] to give the known thiazole derivative **7**[6] with a yield of 58%. When the allene **2a** was allowed to react with sodium cyanoborohydride in MeOH, the formation of the commercially available thiazole **5r** was observed. If **2a** was attacked by more reactive hydrides like $NaBH_4$ in *i*-PrOH or $LiAlH_4$ in Et_2O, the yield of **5r** decreased to 17–18%, and side-products such as **6b** (37%) or *N*-allylmethylamine (25%), were formed, respectively.

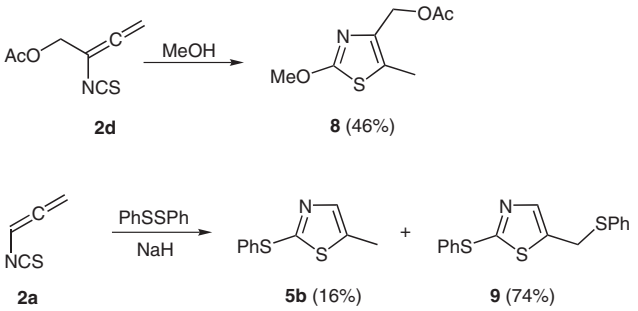


Scheme 2

The synthesis of thiazoles from allenyl isothiocyanates is not limited to the parent compound **2a** but can be transferred to substituted compounds such as **2d**, which was generated with 73% yield through the [3,3]-sigmatropic rearrangement of 4-thiocyanatobut-2-ynyl acetate (**1d**)[13] at 400 °C and 3×10^{-6} mbar. The cumulene **2d** was reacted

with MeOH at room temperature to yield the novel thiazole **8** (Scheme 3).

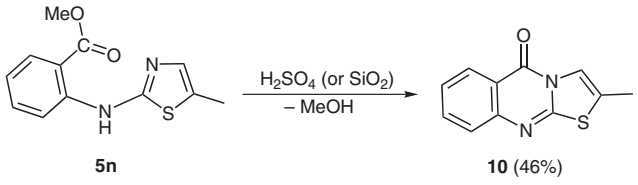
Since allenyl isothiocyanates **2** act as synthetic equivalents of synthons **3**, the negatively charged part of these synthons can be connected not only with a proton but also with alternative electrophiles (Scheme 1). If NaH is reacted with an excess of diphenyl disulfide, a mixture of the nucleophile sodium thiophenolate and the electrophile diphenyl disulfide is formed. Treatment of this mixture with the cumulene **2a** afforded the thiazole **5b** and the main product **9**, which can be explained by nucleophilic attack of thiophenolate at **2a** followed by ring closure and a second nucleophilic attack of the resulting intermediate at the sulfur atom of diphenyl disulfide (Scheme 3).



Scheme 3

Some of the thiazoles formed by conversion of **2** are appropriate for further cyclization reactions. For example, the heterocyclic ester **5n** underwent ring closure in the presence of H_2SO_4 to yield the known[14] compound **10** (Scheme 4). Even on purification over silica gel, **5n** was partially transformed to the product of cyclization, **10**.

In conclusion, we have shown that the reactions of allenyl isothiocyanates with heteroatom nucleophiles can be used successfully for the synthesis of thiazoles. We will demonstrate in a further publication that this concept is transferable to carbon nucleophiles yielding thiazole derivatives by multiple carbon–carbon bond formation.



Scheme 4

^{1}H NMR spectra were recorded at 80 MHz, 200 MHz, 300 MHz and 400 MHz, ^{13}C NMR spectra at 50 MHz, 75 MHz and 100 MHz. Chemical shifts (δ) are reported in ppm downfield from TMS. Coupling constants (*J*) are reported in Hz, and spin multiplicities are indicated by the following symbols: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). IR spectra were recorded in solutions of $CDCl_3$. TLC analyses were performed on Macherey–Nagel precoated silica gel Polygram Sil G/UV$_{254}$ plates and viewed by UV. Chromatography refers to flash chromatography,[15] carried out on Fluka silica gel 60. For the elemental analyses, Vario El (Elementar Analysensystem GmbH) was employed. Mariner 5229 from Applied Biosystems was used for (HR)–MS spectra. The method applied was the electrospray ionization.

Warning: In the case of unstable products like **2a** and **2d**, it was useful to minimize polymerization by dilution of the collected substance with a weighed quantity of an inert solvent before thawing the trap.[2c] Otherwise, a dangerously vigorous reaction is possible since undiluted allenyl isothiocyanates, especially **2a**, tend to undergo spontaneous exothermic polymerization at r.t. Some of the reactions of **2a** with nucleophiles are also highly exothermic. If the potential for evolution of heat is not known, the addition of the reagent should be performed dropwise while the other reaction partner is stirred with cooling.

Some of the thiazole derivatives are already mentioned in short communications.[2a,2b,16]

2-Isopropylsulfanyl-5-methylthiazole (5a)

Propane-2-thiol (**4a**; 300 mL, 247 g, 3.24 mol) was added to isothiocyanatopropa-1,2-diene (**2a**; 6.36 g, 65.6 mmol). After stirring at r.t. for 14 d, the excess of propane-2-thiol was removed, and the crude compound was distilled at 48 °C/0.01 Torr to give **5a** (7.97 g, 46.0 mmol, 70%) as a colorless oil.

IR (CCl_4): 2981, 1443, 1365, 1240, 1153 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.32 (d, ^3J = 6.8 Hz, 6 H, 2 × CH_3), 2.35 (d, ^4J = 0.8 Hz, 3 H, CH_3), 3.63 (sept, ^3J = 6.8 Hz, 1 H, CH), 7.29 (q, ^4J = 0.8 Hz, 1 H, H-4).

^{13}C NMR ($CDCl_3$): δ = 11.9 (q), 23.1 (q, 2 × CH_3), 40.1 (d), 134.9 (s), 140.6 (d), 160.9 (s).

MS: *m*/*z* (%) = 173 (15) [M$^+$], 140 (25), 131 (100), 72 (36), 59 (35).

Anal. Calcd for $C_7H_{11}NS_2$ (173.30): C, 48.52; H, 6.40; N, 8.08. Found: C, 48.54; H, 6.33; N, 8.08.

5-Methyl-2-phenylsulfanylthiazole (5b)

Operating under anhyd N_2, to a suspension of fresh 95% NaH (0.070 g, 2.79 mmol) in anhyd THF (70 mL), thiophenol (**4b**; 0.322 g, 2.92 mmol) and then isothiocyanatopropa-1,2-diene (**2a**) 10% in anhyd THF (0.275 g, 2.83 mmol) were added. After 45 min at r.t., the reaction mixture was diluted with H_2O (10 mL) and extracted with Et_2O (50 mL). The organic layer was dried over $MgSO_4$ and the solvent was removed in vacuo to give the known compound **5b**[4] (0.51 g, 2.46 mmol, 87%) as a yellow liquid.

^{1}H NMR ($CDCl_3$): δ = 2.60 (d, ^4J = 1.2 Hz, 3 H, CH_3), 7.37 (q, ^4J = 1.2 Hz, 1 H, H-4), 7.54–7.57 (m, 5 H, Ph).

^{13}C NMR ($CDCl_3$): δ = 11.8 (q), 128.7 (d), 129.3 (d), 132.5 (s), 132.6 (d), 135.9 (s), 140.9 (d), 162.1 (s).

Synthesis of Thiazoles 5c–e; General Procedure

Phosphites **4c–e** (1.0 equiv) and isothiocyanatopropa-1,2-diene (**2a**) 10% in anhyd THF (1.5 equiv) were added to a suspension of K_2CO_3 (3.0 equiv) in anhyd THF (20 mL). After 2–5 h at r.t., the solvent and excess allene **2a** were removed under vacuum to give thiazoles **5c–e**.

Dimethyl 5-Methylthiazole-2-phosphonate (5c)

Using **2a** (0.66 g, 6.80 mmol), following the general procedure, compound **5c** was obtained (0.78 g, 3.77 mmol, 83%) as a pale yellow oil. Purification was carried out by flash chromatography with EtOAc–CH_2Cl_2 (6:4) as eluent.

IR ($CDCl_3$): 3006, 1448, 1254 (P=O), 1044 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 2.48 (d, ^4J = 1.2 Hz, 3 H, CH_3), 3.76 (d, $^3J_{PH}$ = 11.4 Hz, 6 H, 2 × OCH_3), 7.70 (q, ^4J = 1.2 Hz, 1 H, H-4).

^{13}C NMR ($CDCl_3$): δ = 11.6 (q), 53.6 (q, d, $^2J_{PC}$ = 6.2 Hz, 2 × OCH_3), 140.4 (s, C-5), 144.0 (d, d, $^3J_{PC}$ = 26.2 Hz, C-4), 153.2 (s, d, $^1J_{PC}$ = 245.8 Hz, C-2).

Anal. Calcd for $C_6H_{10}NO_3PS$ (207.19): C, 34.78; H, 4.86; N, 6.76; S, 15.48. Found: C, 34.48; H, 4.77; N, 6.62; S, 15.22

Dibenzyl 5-Methylthiazole-2-phosphonate (5d)

Using **2a** (0.28 g, 2.88 mmol), following the general procedure, compound **5d** was obtained (0.60 g, 1.67 mmol, 88%) as a white solid. Purification was carried out by flash column chromatography with THF–*n*-hexane (4:6) as eluent. Crystallization can be executed from Et_2O and *n*-hexane; mp 45–46 °C.

IR ($CDCl_3$): 3034, 1455, 1264 (P=O), 1001 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 2.47 (d, ^4J = 1.2 Hz, 3 H, CH_3), 5.15 (dd, $^3J_{PH}$ = 12 Hz, ^2J = 8.1 Hz, 2 H, CH_2), 5.16 (dd, $^3J_{PH}$ = 11.7 Hz, ^2J = 8.1 Hz, 2 H, CH_2), 7.26–7.31 (m, 10 H, 2 × Ph), 7.74 (q, ^4J = 1.2 Hz, 1 H, H-4).

^{13}C NMR ($CDCl_3$): δ = 11.5 (q), 68.5 (t, d, $^2J_{PC}$ = 5.6 Hz, 2 × CH_2), 127.7 (d, 4 × Ph), 128.20 (d, 2 × Ph_p), 128.22 (d, 4 × Ph), 135.2 (s, d, $^3J_{PC}$ = 6.8 Hz, 2 × Ph_i), 140.2 (s, C-5), 143.9 (d, d, $^3J_{PC}$ = 26.8 Hz, C-4), 154.0 (s, d, $^1J_{PC}$ = 247.6 Hz, C-2).

Anal. Calcd for $C_{18}H_{18}NO_3PS$ (359.38): C, 60.16; H, 5.05; N, 3.90; S, 8.92. Found: C, 59.98; H, 5.29; N, 3.84; S, 9.03.

Diphenyl 5-Methylthiazolephosphonate (5e)

Using **2a** (0.31 g, 3.20 mmol), following the general procedure, thiazole **5e** was formed (0.64 g, 1.92 mmol, 90%) as a colorless oil. Purification was carried out by flash column chromatography with THF–*n*-hexane (2:8) as eluent.

IR ($CDCl_3$): 3076, 1491, 1275 (P=O), 1026 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 2.45 (d, ^4J = 1.2 Hz, 3 H, CH_3), 7.08–7.26 (m, 10 H, 2 × Ph), 7.79 (q, ^4J = 1.2 Hz, 1 H, H-4).

^{13}C NMR ($CDCl_3$): δ = 11.6 (q), 120.4 (d, d, $^3J_{PC}$ = 4.6 Hz, 4 × Ph_o), 125.3 (d, d, $^4J_{PC}$ = 1.1 Hz, 4 × Ph_m), 129.5 (d, 2 × Ph_p), 141.5 (s, C-5), 144.4 (d, d, $^3J_{PC}$ = 28.4 Hz, C-4), 149.6 (s, d, $^2J_{PC}$ = 7.4 Hz, 2 × Ph_i), 152.0 (s, d, $^1J_{PC}$ = 256.6 Hz, C-2).

Anal. Calcd for $C_{16}H_{14}NO_3PS$ (331.33): C, 58.00; H, 4.26; N, 4.23; S, 9.68. Found: C, 57.60; H, 4.35; N, 4.30; S, 9.94.

2-Methoxy-5-methylthiazole (5f)

Isothiocyanatopropa-1,2-diene (**2a**; 4.31 g, 44.4 mmol) was stirred in MeOH (500 mL) for 5 d at r.t. Then the excess MeOH was removed by distillation, and the crude compound was distilled at 48 °C/26 mbar to give the known compound **5f**[6] (3.96 g, 30.7 mmol, 69%) as a colorless oil. The reaction time can be shortened significantly if **2a** is reacted with MeOH in the presence of a base. For comparison, compound **5f** was also prepared by the known procedure.[6]

^{1}H NMR ($CDCl_3$): δ = 2.30 (d, ^4J = 1.5 Hz, 3 H, CH_3), 4.02 (s, 3 H, OCH_3), 6.75 (q, ^4J = 1.5 Hz, 1 H, H-4).

2-Isopropoxy-5-methylthiazole (5g)

Propan-2-ol (**4g**; 200 mL) was reacted with isothiocyanatopropa-1,2-diene (**2a**; 2.36 g, 24.3 mmol) at r.t. for 91 h. The excess of propan-2-ol was removed at 19.5–20.5 °C/10 Torr, and the crude residue was recondensed at 35 °C/0.007 Torr to afford **5g** (2.0 g, 12.7 mmol, 52%) as a colorless oil.

IR (CCl_4): 2981, 1509, 1467, 1286, 1159 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.34 (d, ^3J = 6.4 Hz, 6 H, 2 × CH_3), 2.24 (d, ^4J = 1.6 Hz, 3 H, CH_3), 5.06 (sept, ^3J = 6.4 Hz, 1 H, CHO), 6.69 (q, ^4J = 1.6 Hz, 1 H, H-4).

^{13}C NMR ($CDCl_3$): δ = 12.3 (q, CH_3), 21.8 (q, 2 × CH_3), 74.7 (d, CHO), 124.7 (s, C-5), 133.3 (d, C-4), 172.6 (s, C-2).

MS: *m*/*z* (%) = 157 (14) [M$^+$], 115 (100), 87 (45), 60 (49), 43 (77).

Anal. Calcd for $C_7H_{11}NOS$ (157.24): C, 53.47; H, 7.05; N, 8.91. Found: C, 52.95; H, 6.84; N, 8.51.

5-Methyl-2-phenoxythiazole (5h)

Isothiocyanatopropa-1,2-diene (**2a**; 11.0 g, 113 mmol) was added to a mixture of phenol (**4h**; 193 g, 2.06 mol) and 40% NaOH (25 mL). After 12 d at r.t., the excess of phenol was removed at 30 °C/0.001 Torr, and the crude compound was distilled at 67.5 °C/0.001 Torr to yield **5h** (14.7 g, 76.9 mmol, 68%) as a colorless oil.

IR (CCl_4): 3065, 2921, 1595, 1481, 1287, 1023 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 2.33 (d, ^4J = 1.3 Hz, 3 H, CH_3), 6.87 (q, ^4J = 1.3 Hz, 1 H, H-4), 7.08–7.49 (m, 5 H, Ph).

^{13}C NMR ($CDCl_3$): δ = 12.2 (q), 119.7 (d, 2 × Ph_o), 125.3 (d, Ph_p), 127.5 (s, C-5), 129.7 (d, 2 × Ph_m), 134.1 (d, C-4), 155.4 (s, Ph_i), 171.2 (s, C-2).

Anal. Calcd for $C_{10}H_9NOS$ (191.25): C, 62.80; H, 4.74; N, 7.32. Found: C, 63.04; H, 5.00; N, 7.37.

5-Methylthiazol-2-ylamine (5i)

Isothiocyanatopropa-1,2-diene (**2a**; 2.41 g, 24.8 mmol) was added to an aqueous solution of NH_3 (200 mL, 25%) and THF (75 mL). After 3 d at r.t., THF was removed under reduced pressure. The aqueous layer was extracted with Et_2O (3 ×), dried ($MgSO_4$) and concentrated to afford **5i** (1.68 g, 14.7 mmol, 59%) as a yellow solid; mp 89–91 °C; Lit.[7] 94–95 °C.

^{1}H NMR ($CDCl_3$): δ = 2.27 (d, ^4J = 1.3 Hz, 3 H, CH_3), 5.50 (br, 2 H, NH_2), 6.69 (q, ^4J = 1.3 Hz, 1 H, H-4).

^{13}C NMR ($CDCl_3$): δ = 11.8 (q), 122.6 (s, C-5), 134.9 (d, C-4), 167.1 (s, C-2).

(5-Methylthiazol-2-yl)propylamine (5j)

Propylamine (**4j**; 1.48 g, 25 mmol) was added slowly under cooling to 10% isothiocyanatopropa-1,2-diene in anhyd Et_2O (2.43 g, 25 mmol). After stirring for 3 d at r.t., the mixture was filtrated, Et_2O was removed under vacuum, and the crude product was recondensed at 80–100 °C/0.005 Torr to yield **5j** (1.75 g, 11.2 mmol, 45%) as a yellow solid. Recrystallization was done from *n*-hexane to give yellow crystals; mp 59 °C.

IR (CCl_4): 3207 (NH), 2966, 1590, 1459, 1338, 1175 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 0.97 (t, ^3J = 7.4 Hz, 3 H, CH_2CH_3), 1.65 (m, 2 H, CH_2CH_3), 2.26 (d, ^4J = 1.5 Hz, 3 H, 5-CH_3), 3.15 (t, ^3J = 7.4 Hz, 2 H, NHCH_2), 6.08 (br s, 1 H, NH), 6.70 (br q, ^4J = 1.5 Hz, 1 H, H-4).

^{13}C NMR ($CDCl_3$): δ = 11.4 (q), 11.9 (q), 22.5 (t), 47.7 (t), 120.2 (s), 135.3 (d), 169.5 (s).

MS: *m*/*z* (%) = 156 (32) [M$^+$], 127 (100), 114 (75), 100 (22), 73 (34).

Anal. Calcd for $C_7H_{12}N_2S$ (156.25): C, 53.81; H, 7.74; N, 17.93. Found: C, 53.77; H, 7.81; N, 17.85.

(5-Methylthiazol-2-yl)phenylamine (5k)

To freshly distilled aniline (100 mL), isothiocyanatopropa-1,2-diene (**2a**; 4.06 g, 41.8 mmol) was added slowly. The reaction mixture was stirred at r.t. for 6 d. The excess of aniline was removed at 50 °C/0.001 Torr, and the residue was crystallized from cyclohexane to give **5k** (6.49 g, 34.1 mmol, 82%) as colorless crystals (mp 116 °C; Lit.[8] 118 °C).

^{1}H NMR ($CDCl_3$): δ = 2.42 (d, ^4J = 1.3 Hz, 3 H, CH_3), 7.01 (q, ^4J = 1.3 Hz, 1 H, H-4), 7.03–7.12 (m, 1 H, Ph_p), 7.34–7.45 (m, 4 H, Ph), 9.92 (br, 1 H, NH).

^{13}C NMR ($CDCl_3$): δ = 11.7 (q), 117.7 (d, 2 × Ph_o), 121.2 (s, C-5), 122.2 (d, Ph_p), 129.3 (d, 2 × Ph_m), 134.7 (d, C-4), 141.1 (s, Ph_i), 164.7 (s, C-2).

(5-Methylthiazol-2-yl)diphenylamine (5l)

Isothiocyanatopropa-1,2-diene (**2a**; 0.99 g, 10.2 mmol) was added dropwise to freshly distilled diphenylamine (20.0 g, 118 mmol) in THF (10 mL). After 14 d at r.t., the solvent was evaporated, and the excess of diphenylamine was removed at 100 °C/0.001 Torr. The crude product was purified by column chromatography with Et_2O–*n*-pentane (1:1) as eluent to afford **5l** (1.08 g, 4.05 mmol, 40%) as a colorless solid; mp 74–75 °C.

^{1}H NMR ($CDCl_3$): δ = 2.26 (d, ^4J = 1.3 Hz, 3 H, CH_3), 6.94 (q, ^4J = 1.3 Hz, 1 H, H-4), 7.00–7.35 (m, 10 H, 2 × Ph).

^{13}C NMR ($CDCl_3$): δ = 11.8 (q), 125.2 (s, C-5), 125.29 (d, 2 × Ph_p), 125.32 (d, 4 × Ph), 129.4 (d, 4 × Ph), 136.2 (d, C-4), 145.5 (s, 2 × Ph_i), 167.7 (s, C-2).

MS: *m*/*z* (%) = 266 (96) [M^+], 265 (100), 225 (27), 77 (58), 51 (96), 50 (27), 39 (32).

Anal. Calcd for $C_{16}H_{14}N_2S$ (266.36): C, 72.15; H, 5.30; N, 10.52. Found: C, 72.28; H, 5.41; N, 10.67.

Methyl (5-Methylthiazol-2-ylamino)acetate (5m)

Freshly distilled glycine methyl ester[9] (**4m**; 0.84 g, 9.44 mmol) was added to 10% isothiocyanatopropa-1,2-diene in anhyd Et_2O (0.76 g, 7.82 mmol) at 0 °C. After 16 h at r.t., the work-up was carried out using water and Et_2O to yield **5m** (0.98 g, 5.26 mmol, 67%) as a yellow solid. Recrystallization from *n*-hexane afforded yellow crystals; mp 88 °C.

IR (CCl_4): 3422 (NH), 2953, 1751 (C=O), 1531, 1439, 1359, 1220 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 2.28 (d, ^4J = 1.2 Hz, 3 H, CH_3), 3.78 (s, 3 H, OCH_3), 4.12 (s, 2 H, CH_2), 5.10 (br s, 1 H, NH), 6.75 (q, ^4J = 1.2 Hz, 1 H, H-4′).

^{13}C NMR ($CDCl_3$): δ = 11.8 (q, CCH_3), 45.9 (t), 52.2 (q, OCH_3), 122.1 (s, C-5′), 135.3 (d, C-4′), 167.1 (s), 170.8 (s).

Anal. Calcd for $C_7H_{10}N_2O_2S$ (186.23): C, 45.15; H, 5.41; N, 15.04. Found: C, 45.36; H, 5.36; N, 15.05.

Methyl 2-(5-Methylthiazol-2-ylamino)benzoate (5n)

Methyl 2-aminobenzoate (**4n**; 4.0 g, 26.5 mmol) was added to a solution of 10% isothiocyanatopropa-1,2-diene (**2a**) in anhyd Et_2O (2.0 g, 20.5 mmol) under cooling. The mixture was concentrated by evaporating about half of the Et_2O and stirred at r.t. for 3 d. The solvent was removed under vacuum, and the crude product was extracted with boiling *n*-hexane to give **5n** (2.86 g, 11.5 mol, 56%) as an orange oil with traces of **4n**. Upon passing this oil through silica gel using *n*-hexane–EtOAc (4:1) as eluent, partial ring closure of **5n** occurred to furnish 2-methyl-5*H*-thiazolo[2,3-*b*]quinazolin-5-one (**10**).

^{1}H NMR ($CDCl_3$): δ = 2.23 (d, ^4J = 1.5 Hz, 3 H, CH_3), 3.82 (s, 3 H, OCH_3), 6.81 (dd, *J* = 8.5 Hz, *J* = 8.2 Hz, 1 H), 6.85 (q, ^4J = 1.5 Hz, 1 H, H-4′), 7.41 (d, ^3J = 8.2 Hz, 1 H), 7.90 (dd, *J* = 8.5 Hz, *J* = 8.2 Hz, 1 H), 8.40 (d, *J* = 8.2 Hz, 1 H), 10.94 (br s, 1 H, NH).

^{13}C NMR ($CDCl_3$): δ = 11.4 (q), 52.0 (q), 112.3 (s), 117.0 (d), 119.6 (d), 124.3 (s), 131.0 (d), 134.7 (d), 136.0 (d), 144.0 (s), 161.5 (s), 166.9 (s).

***N*-(5-Methylthiazol-2-yl)-*N*′,*N*′,*N*″,*N*″-tetramethylguanidine (5o)**

Isothiocyanatopropa-1,2-diene (**2a**; 10%) in anhyd THF (0.539 g, 5.56 mmol) was added dropwise to tetramethylguanidine (0.640 g, 5.56 mmol) in anhyd THF (10 mL) at 0 °C. After 3 h at r.t., the volatile substances were removed at 20 °C/0.001 Torr to yield **5o** (1.12 g, 5.23 mmol, 95%) as a brown oil.

IR (CCl_4): 2920, 1515, 1473, 1386, 1016 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 2.29 (d, ^4J = 1.2 Hz, 3 H, CH_3), 2.81 [s, 12 H, 2 × $N(CH_3)_2$], 6.85 (q, ^4J = 1.2 Hz, 1 H, H-4).

^{13}C NMR ($CDCl_3$): δ = 12.5 (q), 39.7 (q, 4 × CH_3), 125.2 (s), 136.0 (d), 162.2 (s), 171.9 (s).

Anal. Calcd for $C_9H_{16}N_4S$ (212.32): C, 50.91; H, 7.60; N, 26.39; S, 15.10. Found: C, 50.40; H, 7.60; N, 26.49; S, 15.71.

5-(5-Methylthiazol-2-yl)-10,11-dihydro-5*H*-dibenzo[*b*,*f*]azepine (5p)

10,11-Dihydro-5*H*-dibenzo[*b*,*f*]azepine (0.50 g, 2.56 mmol) in anhyd THF (2 mL) was added dropwise to a solution of isopropylmagnesium bromide (calculated to be 0.377 g, 2.56 mmol, prepared from 0.0622 g of Mg and 0.315 g of isopropyl bromide) in anhyd THF (4 mL). The mixture was stirred for 2 h at r.t., and then 10% isothiocyanatopropa-1,2-diene (**2a**) in anhyd THF (0.372 g, 3.84 mmol) was added, over a period of 5 min under N_2 gas at 0 °C. After stirring for 3 h at r.t., Et_2O (15 mL) was added and, then the mixture was washed with sat. aq NH_4Cl (20 mL). The organic layer was separated, and the aqueous layer was extracted with Et_2O (3 × 10 mL). The organic phases were combined and dried ($MgSO_4$). After removal of the solvent, the residue was purified by flash chromatography using Et_2O–*n*-hexane (1:1) as eluent to give **5p** as a pale yellow-green solid (0.261 g, 0.893 mmol, 35%). Crystallization was done from Et_2O and *n*-hexane; mp 119–121 °C.

IR ($CDCl_3$): 1504, 1446, 1324, 1150 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 2.23 (d, ^4J = 1.2 Hz, 3 H, CH_3), 3.10 (s, 4 H, 2 × CH_2), 6.83 (q, ^4J = 1.2 Hz, 1 H, H-4′), 7.24–7.59 (m, 8 H, 8 × Ar-H).

^{13}C NMR ($CDCl_3$): δ = 11.73 (q, CH_3), 30.79 (t, 2 × CH_2), 122.08 (s, C-5′), 127.13 (d, 2 × C), 127.83 (d, 2 × C), 128.64 (d, 2 × C), 130.51 (d, 2 × C), 136.38 (d, C-4′), 136.97 (s, 2 × C), 142.74 (s, 2 × C), 169.59 (s, C-2′).

Anal. Calcd for $C_{18}H_{16}N_2S$ (292.40): C, 73.94; H, 5.52; N, 9.58; S, 10.97. Found: C, 73.40; H, 5.54; N, 9.60; S, 10.61.

1-(5-Methylthiazol-2-yl)-1*H*-indole (5q)

1*H*-Indole (5.85 g, 50 mmol) in anhyd THF (10 mL) was added dropwise to a solution of ethylmagnesium bromide (calculated to be 3.33 g, 25 mmol, prepared from 0.61 g of Mg and 2.72 g of ethyl bromide) in anhyd THF (15 mL) at 0 °C. The mixture was stirred for 90 min at the same temperature, then 10% isothiocyanatopropa-1,2-diene (**2a**) in anhyd Et_2O (1.94 g, 20 mmol) was added at 0–10 °C. After stirring overnight, the mixture was worked up with Et_2O and aq NH_4Cl as usual. The solvent was removed under vacuum, and the crude product was separated from the excess of indole by flash chromatography using EtOAc–*n*-hexane (1:4) as eluent to give **5q** (3.64 g, 17 mmol, 85%). Recrystallization was done from *n*-pentane to afford yellow crystals; mp 44 °C.

IR (CCl_4): 3067, 2922, 1520, 1450, 1348, 1232 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 2.44 (d, ^4J = 1.2 Hz, 3 H, CH_3), 6.77 (d, ^3J = 3.5 Hz, 1 H, H-3), 7.22 (q, ^4J = 1.2 Hz, 1 H, H-4′), 7.23 (m, 1 H, H-5), 7.34 (m, 1 H, H-6), 7.60 (d, ^3J = 3.5 Hz, 1 H, H-2), 7.63 (d, 1 H, H-7), 8.24 (d, ^3J = 8.1 Hz, 1 H, H-4).

^{13}C NMR ($CDCl_3$): δ = 11.6 (q, CH_3), 106.5 (d, C-3), 113.0 (d, C-7), 121.1 (d, C-6), 121.9 (d, C-4), 123.6 (d, C-5), 126.3 (d, C-2), 127.7 (s, C-3a or C-5′), 129.9 (s, C-3a or C-5′), 134.9 (s, C-7a), 136.9 (d, C-4′), 158.6 (s, C-2′).

Anal. Calcd for $C_{12}H_{10}N_2S$ (214.29): C, 67.26; H, 4.70; N, 13.07; S, 14.96. Found: C, 66.96; H, 4.63; N, 12.83; S, 15.42.

5-Methyl-3*H*-thiazol-2-one (6a)
Isothiocyanatopropa-1,2-diene (**2a**; 3.07 g, 31.6 mmol) was added to a solution of NaOH (12.0 g, 300 mmol) in a mixture of H_2O (1200 mL) and THF (1200 mL). After 30 min, the mixture was neutralized with 5% H_2SO_4. The solvent was removed under vacuum, and the crude product was extracted using a Soxhlet apparatus and CH_2Cl_2 for 1 d. After removing the solvent, the product was recrystallized from Et_2O to afford **6a** (3.14 g, 27.3 mmol, 86%) as a colorless solid; mp 137–138 °C (Lit.[6] 144–145 °C).

IR ($CDCl_3$): 3160, 1690, 1660 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 2.12 (d, ^4J = 1.5 Hz, 3 H, CH_3), 6.28 (q, ^4J = 1.5 Hz, 1 H, H-4) 10.19 (br s, 1 H, NH).

^{13}C NMR ($CDCl_3$): δ = 13.7 (q), 116.3 (s), 116.4 (d), 176.1 (s).

MS: *m*/*z* (%) = 115 (100) [M^+], 60 (49), 59 (84), 58 (19), 45 (22).

5-Methyl-3*H*-thiazole-2-thione (6b)
Isothiocyanatopropa-1,2-diene (**2a**; 1.00 g, 10.3 mmol) was added dropwise to a saturated solution of H_2S in a mixture of H_2O (1000 mL) and THF (2000 mL). After stirring for 3 d at r.t., H_2O and THF were removed under reduced pressure. The residue was recrystallized from CH_2Cl_2 to give **6b** (0.72 g, 5.5 mmol, 53%) as a colorless solid; mp 178–180 °C (Lit.[11] 178–179 °C).

^1H NMR ($CDCl_3$): δ = 2.24 (d, ^4J = 1.3 Hz, 3 H, CH_3), 6.72 (q, ^4J = 1.3 Hz, 1 H, H-4), 11.45 (br s, 1 H, NH).

^{13}C NMR ($CDCl_3$): δ = 12.7 (q), 123.5 (d), 128.2 (s), 188.8 (s).

3,5-Dimethyl-3*H*-thiazol-2-one (7)
A solution of **6a** (0.74 g, 6.4 mmol) in EtOH (50 mL) was added at 0 °C to freshly prepared solution of diazomethane[12] in Et_2O (1 M, 50 mL, 50 mmol). After 2 h at this temperature, the cooling bath was removed and the reaction mixture was stored overnight. Thereafter solvents were evaporated under vacuum to give a mixture of the known compound **7**[6] (0.48 g, 3.72 mmol, 58%) and small amounts of **5f** (0.08 g, 0.62 mmol, 10%).

^1H NMR ($CDCl_3$): δ = 2.13 (d, ^4J = 1.3 Hz, 3 H, CH_3), 3.25 (s, 3 H, NCH_3), 6.24 (q, ^4J = 1.3 Hz, 1 H, H-4).

^{13}C NMR ($CDCl_3$): δ = 13.6 (q), 31.7 (q), 113.7 (s), 120.9 (d), 172.0 (s).

5-Methylthiazole (5r)
To a solution of sodium cyanoborohydride (1.89 g, 30 mmol) in MeOH (20 mL), 10% isothiocyanatopropa-1,2-diene (**2a**) in anhyd Et_2O (0.97 g, 10.0 mmol) was added at 5 °C. After 9 d at r.t., the mixture was poured into ice/water and made alkaline using NaOH. Normal work-up with Et_2O led to **5r** (0.46 g, 4.6 mmol, 46%; product commercially available) after removal of the solvent.

^1H NMR ($CDCl_3$): δ = 2.51 (d, ^4J = 1.2 Hz, 3 H, CH_3), 7.58 (q, ^4J = 1.2 Hz, 1 H, H-4), 8.65 (s, 1 H, H-2).

MS: *m*/*z* = 99 [M^+].

2-Isothiocyanatobuta-2,3-dienyl Acetate (2d)
Flash vacuum pyrolysis[2c] of 4-thiocyanato-but-2-ynyl acetate[13] (**1d**; 0.62 g, 3.66 mmol) at 400 °C and 3×10^{-6} mbar (vaporization temperature: 90–100 °C) gave yellow oily **2d** (0.45 g, 2.66 mmol, 73%), which contained only a small amount of **1d**.

IR ($CDCl_3$): 2036 (br, NCS), 1743 (C=O), 1225 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 2.11 (s, 3 H, CH_3), 4.69 (t, ^5J = 2.1 Hz, 2 H, CH_2O), 5.42 (t, ^5J = 2.1 Hz, 2 H, $=CH_2$).

^{13}C NMR ($CDCl_3$): δ = 20.7 (q, CH_3), 63.4 (t, C-1′), 85.6 (t, C-4′), 100.8 (s, C-2′), 138.9 (s, NCS), 170.2 (s, C=O), 207.3 (s, C-3′).

2-Methoxy-5-methylthiazol-4-yl Methyl Acetate (8)
A solution of **2d** (0.42 g, 2.49 mmol) in $CHCl_3$ (20 mL) was added to MeOH (100 mL). The clear yellow solution was stirred for 14 d at r.t. Then the solvent was removed under vacuum, and the yellow oily residue was purified by flash column chromatography using neutral Al_2O_3 and CH_2Cl_2 to yield **8** (0.231 g, 1.15 mmol, 46%) as a slightly yellow oil.

IR (CCl_4): 1735 (C=O), 1536, 1247 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 2.03 [s, 3 H, $C(O)CH_3$], 2.27 (s, 3 H, 5-Me), 3.97 (s, 3 H, OCH_3), 4.89 (s, 2 H, OCH_2).

^{13}C NMR ($CDCl_3$): δ = 11.0 (q, 5-CH_3), 20.8 (q, CH_3), 57.8 (q, OCH_3), 59.1 (t, CH_2O), 124.9 (s), 139.3 (s), 170.7 (s), 171.6 (s).

ESI–MS: *m*/*z* [M + H]$^+$ calcd for $C_8H_{11}NO_3S$: 202.0532; found: 202.0555.

5-Methyl-2-phenylsulfanylthiazole (5b) and 2-Phenylsulfanyl-5-(phenylsulfanylmethyl)thiazole (9)
Operating under anhyd N_2, to a suspension of fresh 95% NaH (0.070 g, 2.79 mmol) in anhyd THF (70 mL), diphenyl disulfide (1.23 g, 5.64 mmol) was added. The mixture was stirred under Ar for 1.5 h at 75 °C, followed by dropwise addition of the isothiocyanatopropa-1,2-diene (**2a**; 0.274 g, 2.82 mmol) in anhyd THF (30 mL) (the color changed to deep red). After stirring for 5 h at 75 °C, the reaction mixture was stirred overnight at r.t. Thereafter it was washed with sat. aq NH_4Cl (150 mL) and extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with water (100 mL) and dried over $MgSO_4$. The solvent was removed in vacuo, and the products were separated by flash chromatography with Et_2O–*n*-hexane (1:2) as eluent to give first **5b** as a yellow oil (0.093 g, 0.45 mmol, 16%) and then **9** as a yellow oil (0.66 g, 2.10 mmol, 74%).

Compound 9
IR (CCl_4): 3080, 2920, 1583, 1478, 1402, 1039 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 4.14 (d, ^4J = 0.9 Hz, 2 H, CH_2), 7.41 (t, ^4J = 0.9 Hz, 1 H, H-4), 7.24–7.58 (m, 10 H, 2 × Ph).

^{13}C NMR ($CDCl_3$): δ = 31.2 (t), 127.2 (d), 128.9 (d), 129.3 (d), 129.6 (d), 130.9 (d), 131.6 (s), 133.4 (d), 134.2 (s), 137.4 (s), 141.5 (d), 165.4 (s).

Anal. Calcd for $C_{16}H_{13}NS_3$ (315.48): C, 60.91; H, 4.15; N, 4.44; S, 30.49. Found: C, 60.65; H, 4.36; N, 4.34; S, 30.69.

2-Methyl-5*H*-thiazolo[2,3-*b*]quinazolin-5-one (10)
To **5n** (0.62 g, 2.50 mmol), still containing some **4n**, concd H_2SO_4 (7 mL) was added. The mixture was stirred for 15 min at 40 °C and then cooled down. Neutralization was carried out by using 10% of aq NaOH solution. The crude sticky product was recrystallized from EtOH to give **10** (0.25 g, 1.16 mmol, 46%) as colorless crystals; mp 182 °C (Lit.[14] 183 °C).

^1H NMR (DMSO-d_6): δ = 2.38 (d, ^4J = 1.5 Hz, 3 H, CH_3), 7.46 (dd, *J* = 8.6, 8.2 Hz, 1 H), 7.59 (d, ^3J = 8.2 Hz, 1 H), 7.79 (br q, ^4J = 1.5 Hz, 1 H), 7.82 (dd, *J* = 8.6, 8.2 Hz, 1 H), 8.19 (d, *J* = 8.2 Hz, 1 H).

^{13}C NMR (DMSO-d_6): δ = 13.1 (q), 116.7, 117.8, 123.2, 125.3, 126.1, 126.6, 134.8, 147.9, 157.5, 158.3.

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