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Synthesis of functionalized thiazoles via attack of heterocyclic nucleophiles on allenyl isothiocyanates☆

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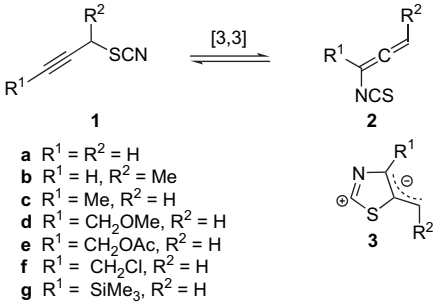
ABSTRACT

New examples of substituted thiazole derivatives carrying different heterocyclic ring systems at C-2 position were prepared via the reaction of several allenyl isothiocyanates with nucleophiles such as imidazoles, pyrazoles, benzimidazoles, indazole, 1,2,3-triazole, 1,2,4-triazole, and 1*H*-benzotriazole. Although these allenyl isothiocyanates are very reactive electrophiles and tend to polymerize, the yield of the thiazole products ranked between modest and very good. The regiochemistry of the reactions was proved by NMR and X-ray studies indicating that the attack of ambident nucleophiles proceeded very selectively. In some cases, however, the products were formed as mixtures of aromatic heterocycles and non-aromatic isomers. The latter could be rearranged to yield the uniform aromatic thiazoles.

1. Introduction

Isothiocyanates are extremely useful in organic synthesis.[2,3] Thus, several methods to prepare such compounds were developed.[3,4] The only access to allenyl isothiocyanates of type **2** is based on the [3,3]-sigmatropic rearrangement of propargyl thiocyanates **1** (Scheme 1).[5] This rearrangement is derived from the well known isomerization of allyl thiocyanate to allyl isothiocyanate.[6] However, the process **1**→**2** can be successfully performed only by the technique of flash vacuum pyrolysis (FVP) because neat (undiluted) cumulenes **2** tend to exothermic spontaneous polymerization even at rt.[5] Whereas allenyl isothiocyanates like **2a** and **2b** can be obtained nearly quantitatively in 100 g batches per day, there are some limitations in other cases such as **2c** and **2e**–**2g**. The yields of **2e** and **2f** are diminished to 73% and 60%, respectively, since the precursors **1e** and **1f** cannot be vaporized without decomposition. Flash vacuum pyrolyses of **1c** or **1g** lead to equilibria with **2c** or **2g**, respectively (ratios **1c**/**2c**=17:83 and **1g**/**2g**=89:11). In the case of **1d**,[7] the analogous process gives rise to a mixture with **1d**/**2d**=4:96 in 95% yield.[8] This equilibrium ratio can be verified by renewed flash vacuum pyrolysis of **2d**, which was separated by liquid chromatography.



Scheme 1.

Recently, treatment of allenyl isothiocyanates **2** with simple nucleophiles was utilized to prepare substituted thiazoles[9] bearing a functional group at the C-2 position.[5] We present now the reactions of the highly reactive cumulenes **2** with the weak nucleophile water and with five-membered heterocycles to reveal regioselectively thiazole derivatives. Thus, the chemistry of **2** illustrates that allenyl isothiocyanates act predominantly as manifold synthetic equivalents of synthons **3**.

2. Results and discussion

2.1. Subsequent reactions of allenyl isothiocyanate (2a) with water

The allenyl isothiocyanate (**2a**) is extremely reactive, as is exemplified by its conversion into 2-diphenylamino-5-methylthiazole

☆ See Ref. 1.

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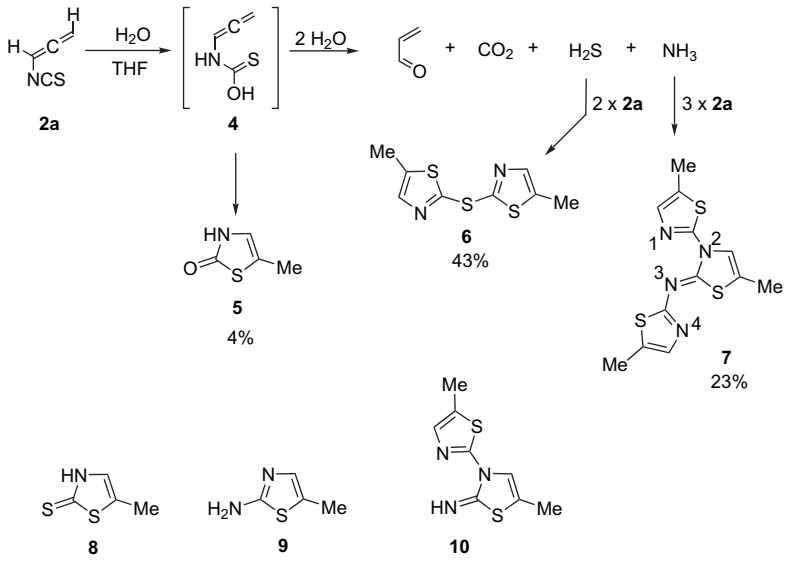


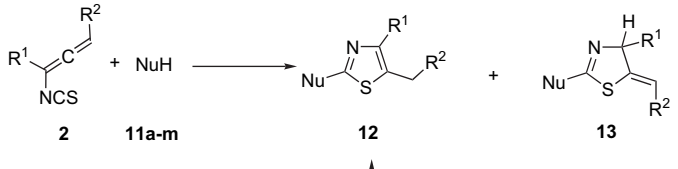
Scheme 2.

with diphenylamine at rt.[5d] Phenyl isothiocyanate is only attacked by this weak nitrogen nucleophile at 280 °C.[10] Thus, it was not surprising that **2a** readily formed heterocyclic products on treatment with water/THF (1:2) already at rt although normal isothiocyanates are known to react so slowly that they can be purified by steam distillation. However, the expected thiazole **5**,[11] which is available from **2a** and diluted aqueous NaOH in 86% yield,[5d] was generated only as a side product with 4% yield (Scheme 2). Instead, the main reactions led to the unexpected compounds **6** and **7**. These products are possibly derived from the intermediate **4**, which is not only able to cyclize to afford **5** but, as a labile thiocarbamic acid, can also decompose to acrolein, carbon dioxide, hydrogen sulfide, and ammonia. The latter two compounds are more nucleophilic than water and subsequently react with **2a** to afford the major products **6** and **7** via the intermediates **8** as well as **9** and **10**, respectively. In accordance with this reaction pathway, **6** can be prepared in higher yield (77%) from **2a** and H_2S/H_2O or in 99.6% yield from **2a** and thiazole **8**.[12] Similarly, the synthesis of **7** was performed with **2a** and less than stoichiometric quantities of aqueous ammonia (88% yield) or with **2a** and **9**[13] (90%). The intermediate for these reactions, namely compound **10**, can be isolated and treated with **2a** to give **7**. The formation of **10** from **9** shows that thiazole derivatives can be produced selectively and effectively by the attack of heterocyclic nitrogen atoms on allenyl isothiocyanates. Thus, we were encouraged to investigate the reaction of these cumulenes with further nitrogen heterocycles.

2.2. Reactions of allenyl isothiocyanates with azole nucleophiles

A new family of substituted thiazole derivatives carrying different heterocyclic ring systems at C-2 position was prepared via the reaction of the allenyl isothiocyanates **2a–c** and **2d**[8] with the imidazoles **11a–c**, pyrazoles **11d–g**,[14,15] benzimidazoles **11h–j**, indazole (**11k**), 1,2,3-triazole (**11l**), benzotriazole (**11m**), and 1,2,4-triazole (**11n**) (Table 1 and Scheme 3). Due to the symmetrical structure of the corresponding azole reagents, several transformations afforded a single aromatic thiazole product exclusively in good to excellent yields, such as **12aa**, **12ca**, **12ad**, **12cd**, **12dd**, **12ah**, and **12aj**. In the case of **11i**, only the ring nitrogen, but not the primary amine, attacked the allenyl isothiocyanate (**2a**) to induce formation of thiazole **12ai**. In order to maintain the favorable aromatic benzo unit, indazole (**11k**) and benzotriazole (**11m**) yielded selectively the products **12ak** and **12am**, respectively, bearing the thiazole ring at N-1 instead of N-2. Although **11l** is known[16] to furnish mixtures of 1*H*-1,2,3-triazoles and 2*H*-1,2,3-triazoles by treatment with common electrophiles like alkyl halides or

Table 1
Reactions of allenyl isothiocyanates **2a–d** with nucleophiles **11a–m**

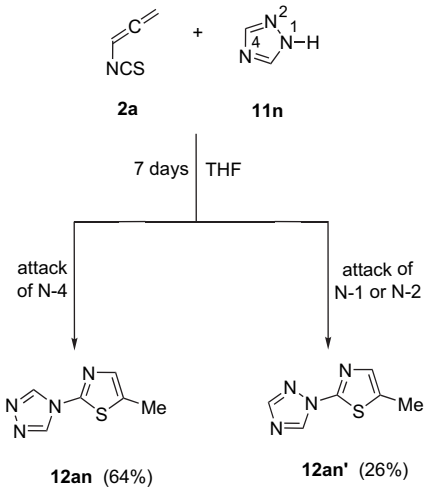


a $R^1 = R^2 = H$
b $R^1 = H$; $R^2 = Me$
c $R^1 = Me$; $R^2 = H$
d $R^1 = CH_2OMe$; $R^2 = H$

Allene **2**	Nucleophile **11**[a]	Solvent	Reaction time	**12**	Yield (%)	**13**	Yield (%)
a	**a**	THF	1 h	**aa**	80	—	—
b	**a**	THF	5 days	**ba**	56	**ba**	25
c	**a**	THF	1 day	**ca**	80	—	—
d	**a**	THF	2 h	**da**	74	**da**	13
a	**b**	THF	1 h	**ab**	80	**ab**	10
d	**b**	THF	1 h	**db**	79	**db**	3
a	**c**	DMF	5 days	**ac**	68	—	—
a	**d**	THF	5 h	**ad**	90	—	—
b	**d**	THF	6 days	**bd**	19	**bd**	27
c	**d**	THF	3 days	**cd**	77	—	—
d	**d**	THF	2 days	**dd**	91	—	—
a	**e**	CH_2Cl_2	2 h	**ae**	49	**ae**	33
d	**e**	CH_2Cl_2	5 h	**de**	50	**de**	30
a	**f**	$CHCl_3$	24 h	**af**	66	**af**	22
d	**f**	$CHCl_3$	24 h	**df**	39	**df**	46
a	**g**	CH_2Cl_2	3 h	**ag**	91	—	—
d	**g**	CH_2Cl_2	6 h	**dg**	88	—	—
a	**h**	THF	3 h	**ah**	85	—	—
a	**i**	THF	30 min	**ai**	83	—	—
a	**j**	THF	1 day	**aj**	82	—	—
d	**j**	THF	40 h	**dj**	76	**dj**	17
a	**k**	THF	24 h	**ak**	95	—	—
a	**l**	THF	7 days	**al**	69	—	—
a	**m**	THF	7 days	**am**	86	—	—

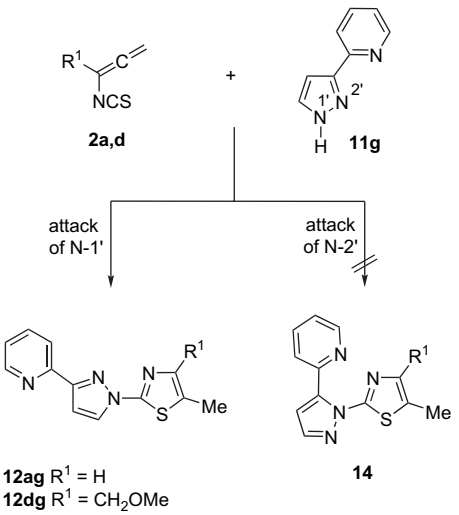
[a] Nucleophiles **11**: 1*H*-imidazole (**11a**); 2-ethyl-4-methyl-1*H*-imidazole (**11b**); 4-nitro-1*H*-imidazole (**11c**); 1*H*-pyrazole (**11d**); 3,5-dimethyl-1*H*-pyrazole (**11e**); 3,4,5-trimethyl-1*H*-pyrazole (**11f**);[14] 2-(1*H*-pyrazol-3-yl)-pyridine (**11g**);[15] 1*H*-benzimidazole (**11h**); 1*H*-benzimidazol-2-ylamine (**11i**); 2-ethyl-1*H*-benzimidazole (**11j**); 1*H*-indazole (**11k**); 1*H*-1,2,3-triazole (**11l**), and 1*H*-benzotriazole (**11m**).

acylating compounds, the reaction with **2a** led to the sole product 1-(5-methylthiazol-2-yl)-1*H*-1,2,3-triazole (**12al**). In contrast to that the analogous transformation of **11n** gave a mixture of **12an** and **12an′** as shown in Scheme 3. The assignment of the heterocycles **12an** and **12an′** was easily performed by NMR spectroscopy.

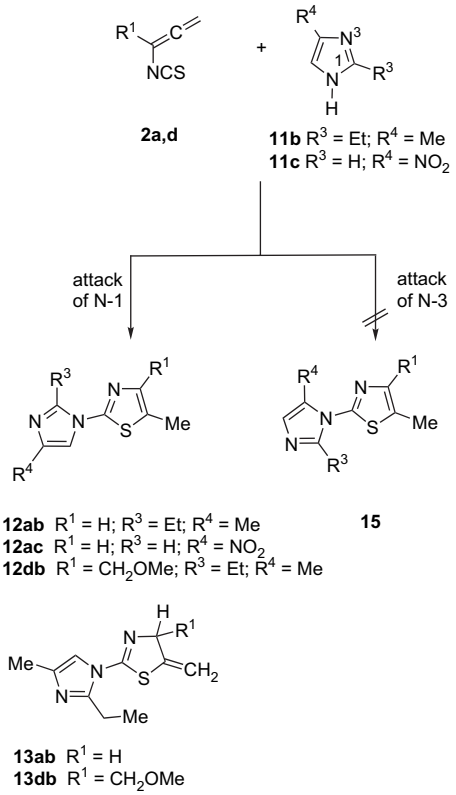


Scheme 3.

In the case of less symmetrical azole nucleophiles such as **11b**, **11c**, and **11g**, two non-equivalent nitrogen atoms could attack the allenyl isothiocyanate **2** resulting in two different aromatic thiazole derivatives as depicted in Schemes 4 and 5. Since we always obtained only one aromatic product in each transformation, we assumed that the sterically less hindered nitrogen atom, namely N-1 of **11b**,**c** and N-1′ of **11g**, should bind to the electrophilic carbon of the isothiocyanate **2**. However, we were not able to exclude the alternative structures **14** and **15** by NMR methods. Fortunately, a sample of **12ag** was suitable to get the molecular structure from single-crystal X-ray diffraction analysis confirming the supposed constitution.[17] The strongly electron-withdrawing nitro group of **11c** may have a dominating electronic influence on the nucleophilicity of the imidazole nitrogen atoms, which is different to the steric effect and overcompensates the latter. But also in the case of **12ac**, single-crystal X-ray diffraction analysis verified the assumed structure as shown in Figure 1.[18] Thus, we presume that the sterically less hindered nitrogen atom of **11b**, **11c**, and **11g** will generally be favored to attack the allenyl isothiocyanate **2**.



Scheme 4.



Scheme 5.

Treatment of cumulene **2** with azoles **11** did not only afford the aromatic heterocycles **12** but also the 5-methylenethiazole derivatives **13**. In the case of **13bd** and **13df**, these non-aromatic thiazoles represent even the main products as depicted in Table 1. Although all compounds **13** are stable at −18 °C for several months, they were converted quantitatively into the more favorable aromatic tautomers **12** in the presence of chloroform, for example, when **13** was stored in $CDCl_3$ solution in an NMR tube.[19] The rate of this isomerization was found to be concentration dependent. Separation of **12** and **13** by flash chromatography using silica gel was also accompanied by the rearrangement to **12**, thus hampering the isolation of **13**. On the other hand, the directed aromatization **13**→**12** led to uniform products. Furthermore, this reaction confirmed that only the less sterically hindered nitrogen atom of **11b** attacked the allenyl isothiocyanates **2** to form the products **13ab** and **13db**.

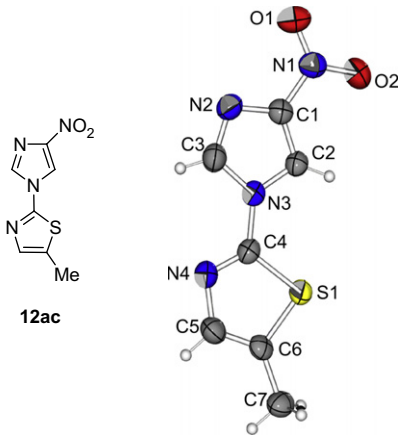


Figure 1. Molecular structure of **12ac**.

3. Conclusion

A new family of substituted thiazoles bearing different types of azole heterocycles at C-2 position was prepared via the reaction of these heterocycles with highly reactive allenyl isothiocyanates. The steric as well as the electronic effects of the azole nucleophiles controlled the position of the introduced thiazole ring. The resulting heterocyclic products may have biological activities and will be subjected to further studies.

4. Experimental

4.1. General

^{1}H NMR spectra were recorded at 300 MHz, ^{13}C NMR spectra at 75 MHz, and ^{15}N NMR spectra at 40 MHz. Chemical shifts (δ) are reported in parts per million (ppm) downfield from TMS. Coupling constants (J) are reported in hertz (Hz) and spin multiplicities are indicated by the following symbols: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). Infrared spectra were recorded as solutions in $CDCl_3$. TLC was performed on Macherey–Nagel precoated silica gel Polygram Sil G/UV$_{254}$ plates and viewed by UV. Flash chromatography[20] was carried out on Fluka silica gel 60. HPLC separations were conducted under isocratic flow with distilled and degassed diethyl ether. A Knauer model 64 HPLC pump equipped with Merck LiChrospher Si 60, 5 μm (∅ 20 mm, l=20 cm) column, and UV detector (λ=254 nm) was utilized. For elemental analyses, Vario El (Elementar Analysensystem GmbH) was employed. MS data (70 eV, electron impact) resulted from Hewlett–Packard spectrometer 5988 A. Mariner 5229 from Applied Biosystems was used for HRMS utilizing the method of electrospray ionization.

Warning. In the case of unstable allenyl isothiocyanates **2**, it was useful to minimize polymerization by dilution of the collected substance with a weighed quantity of an inert solvent before thawing the trap.[5c,d] Otherwise, a dangerously vigorous reaction is possible since undiluted allenyl isothiocyanates, especially **2a**, tend to spontaneous strongly exothermic polymerization at rt. Some of the reactions of **2** with nucleophiles are also highly exothermic. If the evolution of heat was not known, the addition of the reagent was performed dropwise while the other reaction partner was stirred with cooling.

4.2. Flash vacuum pyrolysis of 1-methoxy-4-thiocyanatobut-2-yne (1d) to generate 3-isothiocyanato-4-methoxybuta-1,2-diene (2d)

The flash vacuum pyrolysis[21] of 1-methoxy-4-thiocyanatobut-2-yne[7] (**1d**) (0.10 g, 0.71 mmol) was performed at 400 °C and 10^{-5} Torr (vaporization temperature: 70–80 °C) to give a mixture of **1d** and 3-isothiocyanato-4-methoxybuta-1,2-diene (**2d**) (0.095 g, 0.674 mmol, 95%) with thermal equilibrium ratio of 4% and 96% of **1d** and **2d**, respectively. The unstable allenyl isothiocyanate **2d** was separated by flash chromatography using *n*-hexane and diethyl ether (7:3). The following flash vacuum pyrolysis of pure **2d** at 400 °C and 10^{-5} Torr yielded a mixture of **1d** and **2d** with the same ratio of 4:96, respectively. IR ($CDCl_3$): 2007 (NCS) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ=3.35 (s, 3H, OCH_3), 4.05 (t, ^5J=2.1 Hz, 2H, OCH_2), 5.34 (t, ^5J=2.2 Hz, 2H, =CH_2). ^{13}C NMR ($CDCl_3$): δ=57.64 (q, OCH_3), 72.31 (t, OCH_2), 84.58 (t, C-1), 101.67 (s, C-3), 139.20 (s, NCS), 206.80 (s, C-2).

4.3. Reaction of isothiocyanatopropa-1,2-diene (2a) with water

To H_2O (250 mL) and THF (500 mL), isothiocyanatopropa-1,2-diene (**2a**) (10.0 g, 103.1 mmol) was added, and the mixture was stirred for 21 h at rt. The solvents were removed at 50 °C/26 mbar, and the residue was purified by column chromatography (silica gel, 50×3 cm) using CH_2Cl_2/Et_2O (1:1) to reveal the products in the order **7**, **6**, and **5**.

4.3.1. 5-Methyl-3H-thiazol-2-one (5)

Yield: 0.49 g, 4.3 mmol, 4%, colorless solid; mp 137–138 °C (lit.[11] 144–145 °C), IR ($CDCl_3$): 3160, 1690, 1660 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ=2.12 (d, ^4J=1.5 Hz, 3H, CH_3), 6.28 (q, ^4J=1.5 Hz, 1H, H-4), 10.19 (br, 1H, 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).

4.3.2. Bis(5-methylthiazol-2-yl) sulfide (6)

Yield: 3.41 g, 15.0 mmol, 43.5%, colorless solid; mp: 51 °C. ^{1}H NMR ($CDCl_3$): δ=2.42 (d, ^4J=1.2 Hz, 3H, CH_3), 7.44 (q, ^4J=1.2 Hz, 1H, H-4). ^{13}C NMR ($CDCl_3$): δ=11.98 (q, CH_3), 138.22 (s, C-5), 141.45 (d, C-4), 156.63 (s, C-2). MS, m/z (%) 228 (100) [M]$^+$, 86 (57), 72 (70), 71 (70), 59 (56). Anal. Calcd for $C_8H_8N_2S_3$ (228.35): C, 42.08; H, 3.53; N, 12.27; S, 42.12. Found: C, 41.97; H, 3.47; N, 12.20; S, 42.23.

4.3.3. (5,5′-Dimethyl-[2,3′-bithiazolyl]-2′-ylidene)-(5-methylthiazol-2-yl)-amine (7)

Yield: 1.81 g, 5.90 mmol, 23%, yellow solid; mp: 180 °C. ^{1}H NMR ($CDCl_3$): δ=2.42 (d, ^4J=1.5 Hz, 3H, CH_3), 2.40 (d, ^4J=1.2 Hz, 3H, CH_3), 2.43 (d, ^4J=1.2 Hz, 3H, CH_3), 7.15 (q, ^4J=1.2 Hz, 1H, =CH), 7.17 (q, ^4J=1.2 Hz, 1H, =CH), 7.65 (q, ^4J=1.5 Hz, 1H, =CH). ^{13}C NMR ($CDCl_3$): δ=11.46 (q, CH_3), 12.32 (q, CH_3), 12.90 (q, CH_3), 118.20 (s, =C), 118.39 (d, =CH), 128.12 (s, =C), 130.14 (s, =C), 134.59 (d, =CH), 136.19 (d, =CH), 154.26 (s, N=C), 154.35 (s, N=C), 167.69 (s, N=C). ^{15}N NMR (DMSO-d_6): δ=−218.60 (d, ^2J=4 Hz, N-2), −176.65 (s, N-3), −101.95 (d, ^2J=11 Hz, N-1 or N-4), −101.79 (d, ^2J=10 Hz, N-4 or N-1). MS, m/z (%) 308 (100) [M]$^+$, 151 (18), 125 (17), 72 (22), 71 (27), 59 (22). Anal. Calcd for $C_{12}H_{12}N_4S_3$ (308.43): C, 46.73; H, 3.92; N, 18.17; S, 31.18. Found: C, 46.71; H, 4.05; N, 17.98; S, 31.05. We do not have direct evidence for the (*Z*)-stereochemistry of **7** (Scheme 2). But intramolecular steric hindrance should be highly unfavorable in (*E*)-**7**. Furthermore, we were able to verify (*Z*)-stereochemistry by single-crystal X-ray diffraction analysis in the case of a similar compound.[8]

4.4. Reaction of isothiocyanatopropa-1,2-diene (2a) with hydrogen sulfide

To a solution of hydrogen sulfide in water (142 mL, 0.0725 M, titrated with NaOH) and THF (284 mL), isothiocyanatopropa-1,2-diene (**2a**) (1.99 g, 20.5 mmol) was added and the mixture was stirred for 8 days at rt. Thereafter, THF was removed under vacuum, and the residue was extracted with CH_2Cl_2, dried ($MgSO_4$), and concentrated to afford bis(5-methylthiazol-2-yl) sulfide (**6**) (1.81 g, 7.9 mmol, 77%).

4.5. Reaction of isothiocyanatopropa-1,2-diene (2a) with 5-methyl-3*H*-thiazole-2-thione (8)

To a solution of 5-methyl-3*H*-thiazole-2-thione (**8**)[12] (2.70 g, 20.6 mmol) in THF (100 mL), H_2O (50 mL) was added followed by the addition of isothiocyanatopropa-1,2-diene (**2a**) (2.00 g, 20.6 mmol). After stirring for 14 days at rt, THF was removed under vacuum and the residue was extracted with CH_2Cl_2, dried ($MgSO_4$), and concentrated to reveal bis(5-methylthiazol-2-yl) sulfide (**6**) (4.86 g, 20.5 mmol, 99.6%).

4.6. Reaction of isothiocyanatopropa-1,2-diene (2a) with aqueous ammonia

To a mixture of aqueous ammonia (85 mL, 11.6 mmol, 0.137 M) and THF (170 mL), isothiocyanatopropa-1,2-diene (**2a**) (5.04 g, 52.0 mmol) was added and the solution was stirred for 10 days at rt.

Then, THF was removed under vacuum and the residue was extracted with CH_2Cl_2, dried ($MgSO_4$), and concentrated. The crude product was recrystallized from Et_2O/CH_2Cl_2 to furnish (5,5′-dimethyl-[2,3′-bithiazolyl]-2′-ylidene)-(5-methylthiazol-2-yl)-amine (**7**) (3.15 g, 10.2 mmol, 88%).

When the reaction of **2a** with aqueous ammonia was performed similarly but using a smaller amount of **2a** (3.14 g, 32.4 mmol instead of 5.04 g), analogous work-up gave **7** (1.65 g, 50%), **9**[13] (0.41 g, 11%), and **10** (0.76 g, 22%). Compound **10** could be enriched by chromatography to afford a yellow solid. However, we were not able to separate it from the other products completely.

*4.6.1. 5,5′-Dimethyl-2′-imino-[2,3′-bithiazolyl] (**10**)*

^{1}H NMR ($CDCl_3$): δ=2.14 (d, ^4J=1.6 Hz, 3H, CH_3), 2.42 (d, ^4J=1.3 Hz, 3H, CH_3), 7.13 (q, ^4J=1.3 Hz, 1H, =CH), 7.34 (q, ^4J=1.6 Hz, 1H, =CH), 7.70 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ=11.32 (q, CH_3), 13.19 (q, CH_3), 113.77 (s), 119.27 (d), 128.49 (s), 134.26 (d), 154.47 (s), 159.87 (s). MS, *m*/*z* (%) 211 (100) $[M]^+$, 170 (36), 125 (32), 99 (71), 71 (35), 59 (59).

4.7. Reaction of isothiocyanatopropadiene (2a) with 9

To a solution of **9**[13] (1.18 g, 10.3 mmol) in THF (100 mL), water (50 mL) and isothiocyanatopropadiene (**2a**) (2.00 g, 20.6 mmol) were added. The mixture was stirred for 17 days at rt. After removal of THF under vacuum, the residue was extracted with CH_2Cl_2, dried ($MgSO_4$), and concentrated to yield **7** (2.87 g, 90%).

4.8. General procedure for the synthesis of thiazoles from allenyl isothiocyanates 2 and azoles 11

Isothiocyanatopropa-1,2-diene **2a**, **2b**, **2c**, or **2d** (each 10% in dry THF, 1.50 equiv) was added to azoles **11a**–**n** (1.00 equiv) dissolved in 5 mL of a dry appropriate solvent (for azoles **11a**–**m**, see Table 1; for azole **11n**, see Scheme 3). After the reaction was completed, the solvent was removed under vacuum. If necessary, the crude products were separated by flash chromatography using diethyl ether for **12ca**, acetone and *n*-hexane (3:7) for **12da**/**13da**, acetone and *n*-hexane (1:4) for **12ab**/**13ab** and **12ac**, acetone and *n*-hexane (2:3) for **12db**/**13db**, diethyl ether and *n*-hexane (2:3) for **12bd**/**13bd**, ethyl acetate and *n*-hexane (2:1) for **12cd**, diethyl ether and *n*-hexane (1:1) for **12dd**, diethyl ether and *n*-hexane (1:4) for **12ae**/**13ae**, **12af**/**13af**, and **12ak**, ethyl acetate and *n*-hexane (3:7) for **12de**/**13de** and **12df**/**13df**, ethyl acetate and dichloromethane (3:7) for **12ag** and **12dg**, ethyl acetate and dichloromethane (2:3) for **12dj**/**13dj**, and finally acetone and *n*-hexane (1:2) for **12an**/**12an′**. Upon separation by flash chromatography, the non-aromatic product was eluted before the aromatic one in all cases.

*4.8.1. 2-Imidazol-1-yl-5-methylthiazole (**12aa**)*

Yield: 0.66 g (80%), yellow crystals; mp: 59–60 °C (from acetone). ^{1}H NMR ($CDCl_3$): δ=2.47 (d, ^4J=1.2 Hz, 3H, CH_3), 7.15 (d, ^3J=0.9 Hz, 1H, CH), 7.21 (d, ^3J=0.9 Hz, 1H, =CH), 7.44 (q, ^4J=1.2 Hz, 1H, H-4), 8.09 (s, 1H, H-2′). ^{13}C NMR ($CDCl_3$): δ=11.88 (q, CH_3), 117.44 (d, C=CH), 130.53 (d, C=CH), 130.73 (s, C-5), 135.18 (d, C=CH), 137.53 (d, C=CH), 155.31 (s, C-2). Anal. Calcd for $C_7H_7N_3S$ (165.22): C, 50.88; H, 4.27; N, 25.43; S, 19.40. Found: C, 50.39; H, 4.05; N, 25.44; S, 19.23.

*4.8.2. 5-Ethyl-2-imidazol-1-yl-thiazole (**12ba**) and 5-ethylidene-2-imidazol-1-yl-4,5-dihydrothiazole (**13ba**)*

Following the general procedure, thiazoles **12ba** (0.50 g, 2.79 mmol, 56%) and **13ba** (0.22 g, 1.23 mmol, 25%) were separated by HPLC and obtained as yellow oils. Compound **12ba** was recrystallized from *n*-pentane whereas thiazole **13ba** was recrystallized from *n*-hexane.

*Compound **12ba***. Mp: 31–32 °C. ^{1}H NMR ($CDCl_3$): δ=1.28 (t, ^3J=7.5 Hz, 3H, CH_3), 2.80 (q, ^3J=7.5 Hz, 2H, CH_2), 7.11 (d, ^4J=1.2 Hz, 1H, =CH), 7.19 (d, ^3J=1.2 Hz, 1H, =CH), 7.41 (t, ^4J=1.5 Hz, 1H, =CH), 8.06 (s, 1H, =CH). ^{13}C NMR ($CDCl_3$): δ=15.61 (q), 20.41 (t), 117.41 (d), 130.41 (d), 135.17 (d), 135.86 (d), 138.44 (s), 155.11 (s). Anal. Calcd for $C_8H_9N_3S$ (179.24): C, 53.61; H, 5.06; N, 23.44; S, 17.89. Found: C, 53.22; H, 5.04; N, 23.35; S, 17.63.

*Compound **13ba***. Mp: 56–57 °C. ^{1}H NMR ($CDCl_3$): δ=1.73 (dt, ^3J=6.6 Hz, ^5J=2.4 Hz, 3H, CH_3), 4.89 (m, 2H, CH_2), 5.64 (qt, ^3J=6.6 Hz, ^4J=2.4 Hz, 1H, =C*H*–CH_3), 7.09 (d, ^3J=1.2 Hz, 1H, =CH), 7.49 (d, ^3J=1.2 Hz, 1H, =CH), 7.99 (s, 1H, =CH). ^{13}C NMR ($CDCl_3$): δ=18.21 (q), 66.09 (t), 115.79 (d), 117.51 (d), 130.53 (d), 136.21 (d), 137.25 (s), 151.31 (s). ESI-MS (*m*/*z*) calcd for $C_8H_9N_3S$ $[M+H]^+$: 180.0590. Found: 180.0560. We do not have direct evidence for the (*Z*)-stereochemistry of **13ba**, see Table 1. But in the case of similar compounds,[5c] we were able to verify this stereochemistry by ^{1}H NMR NOE experiments.

*4.8.3. 2-Imidazol-1-yl-4,5-dimethylthiazole **12ca***

Yield: 0.59 g (80%), yellow crystals; mp: 62–63 °C (from diethyl ether). ^{1}H NMR ($CDCl_3$): δ=2.29 (s, CH_3), 2.34 (s, CH_3), 7.13 (d, ^3J=0.9 Hz, 1H, =CH), 7.41 (d, ^3J=0.9 Hz, 1H, =CH), 8.07 (s, 1H, =CH). ^{13}C NMR ($CDCl_3$): δ=11.18 (q, CH_3), 14.61 (q, CH_3), 117.44 (d), 122.97 (s), 130.50 (d), 135.22 (d), 145.82 (s), 152.62 (s). Anal. Calcd for $C_8H_9N_3S$ (179.24): C, 53.60; H, 5.06; N, 23.44; S, 17.88. Found: C, 53.20; H, 5.23; N, 23.34; S, 17.67.

*4.8.4. 2-Imidazol-1-yl-4-methoxymethyl-5-methylthiazole (**12da**) and 2-imidazol-1-yl-4-methoxymethyl-5-methylene-4,5-dihydrothiazole (**13da**)*

Following the general procedure, thiazoles **12da** (0.45 g, 2.15 mmol, 74%) and **13da** (0.08 g, 0.383 mmol, 13%) were obtained as white solid (recrystallization from acetone and *n*-hexane) and yellow semi-solid, respectively.

*Compound **12da***. Mp: 43–44 °C. ^{1}H NMR ($CDCl_3$): δ=2.48 (s, 3H, CH_3), 3.44 (s, 3H, OCH_3), 4.45 (s, 2H, OCH_2), 7.16 (d, ^3J=0.9 Hz, 1H, =CH), 7.45 (d, ^3J=0.9 Hz, 1H, =CH), 8.12 (s, 1H, =CH). ^{13}C NMR ($CDCl_3$): δ=10.89 (q), 58.18 (q), 67.05 (t), 117.37 (d), 128.42 (s), 130.32 (d), 135.10 (d), 145.90 (s), 153.27 (s). Anal. Calcd for $C_9H_{11}N_3OS$ (209.27): C, 51.65; H, 5.30; N, 20.08; S, 15.32. Found: C, 51.82; H, 5.28; N, 20.17; S, 15.21.

*Compound **13da***. ^{1}H NMR ($CDCl_3$): δ=3.43 (s, 3H, O–CH_3), 3.78 (m, 2H, O–CH_2, diastereotopic protons), 5.18 (m, 1H, CH), 5.43 (m, 2H, =CH_2, non-equivalent protons), 7.11 (dd, ^4J=0.9 Hz, ^3J=1.5 Hz, 1H, =CH), 7.26 (d, ^4J=0.9 Hz, 1H, =CH), 7.43 (t, ^3J=1.5 Hz, 1H, =CH). ^{13}C NMR ($CDCl_3$): δ=59.17 (q), 75.10 (t), 77.37 (d), 106.89 (t), 117.39 (d), 130.23 (d), 135.99 (d), 146.24 (s), 150.79 (s). ESI-MS (*m*/*z*) calcd for $C_9H_{11}N_3OS$ $[M+H]^+$: 210.0696. Found: 210.0637.

*4.8.5. 2-(2-Ethyl-4-methylimidazole-1-yl)-5-methylthiazole (**12ab**) and 2-(2-ethyl-4-methylimidazol-1-yl)-5-methylene-4,5-dihydrothiazole (**13ab**)*

Following the general procedure, thiazoles **12ab** (0.63 g, 3.04 mmol, 80%) and **13ab** (0.08 g, 0.386 mmol, 10%) were obtained as yellow oils.

*Compound **12ab***. ^{1}H NMR ($CDCl_3$): δ=1.28 (t, ^3J=7.5 Hz, 3H, CH_3), 2.19 (d, ^4J=1.2 Hz, 3H, CH_3), 2.43 (d, ^4J=1.2 Hz, 3H, CH_3), 2.94 (q, ^3J=7.5 Hz, 2H, CH_2), 6.91 (q, ^4J=1.2 Hz, 1H, =CH), 7.21 (q, ^4J=1.2 Hz, 1H, =CH). ^{13}C NMR ($CDCl_3$): δ=11.90 (q), 11.98 (q), 13.33 (q), 21.76 (t), 115.77 (d), 131.83 (s), 137.23 (s), 137.56 (d), 149.41 (s), 155.74 (s). ESI-MS (*m*/*z*) calcd for $C_{10}H_{13}N_3OS$ $[M+H]^+$: 208.0851. Found: 208.0822.

*Compound **13ab***. ^{1}H NMR ($CDCl_3$): δ=1.27 (t, ^3J=7.5 Hz, 3H, CH_3), 2.15 (d, ^4J=1.2 Hz, 3H, CH_3), 2.95 (q, ^3J=7.5 Hz, 2H, CH_2), 4.95 (t, ^4J=3.0 Hz, 2H, =CH_2), 5.25 (m, 2H, CH_2), 6.75 (q, ^4J=1.2 Hz, 1H, =CH). ^{13}C NMR ($CDCl_3$): δ=11.77 (q), 13.27 (q), 21.85 (t), 68.11 (t),

104.58 (t), 115.09 (d), 137.14 (s), 146.26 (s), 150.73 (s), 151.83 (s). ESI-MS (m/z) calcd for $C_{10}H_{13}N_3OS$ $[M+H]^+$: 208.0903. Found: 208.0890.

4.8.6. 2-(2-Ethyl-4-methylimidazol-1-yl)-4-methoxymethyl-5-methylthiazole (**12db**) and 2-(2-ethyl-4-methylimidazol-1-yl)-4-methoxymethyl-5-methylene-4,5-dihydrothiazole (**13db**)

Following the general procedure, thiazoles **12db** (0.90 g, 3.59 mmol, 79%) and **13db** (0.03 g, 0.136 mmol, 3%) were obtained as orange and yellow oils, respectively.

Compound ***12db***. IR ($CDCl_3$): 1588 (C=C), 1401 (C=N), 1334 (S–C), 1070 (C–O–C) cm^{-1}. ^1H NMR ($CDCl_3$): δ=1.21 (t, ^3J=7.5 Hz, 3H, CH_2CH_3), 2.10 (s, 3H, Me-5), 2.36 (d, ^4J=1.2 Hz, 3H, Me-4′), 2.85 (q, ^3J=7.5 Hz, 2H, CH_2CH_3), 3.32 (s, 3H, OMe), 4.36 (s, 2H, OCH_2), 6.86 (q, ^4J=1.2 Hz, 1H, H-5′). ^{13}C NMR ($CDCl_3$): δ=10.74 (q, Me), 11.73 (q, Me), 13.12 (q, Me), 21.54 (t, CH_2CH_3), 58.02 (q, OMe), 67.16 (t, OCH_2), 115.53 (d, C-5′), 129.51 (s), 136.92 (s), 145.82 (s), 149.07 (s), 153.40 (s). Anal. Calcd for $C_{12}H_{17}N_3OS$ (251.35): C, 57.34; H, 6.82; N, 16.72; S, 12.76. Found: C, 57.12; H, 6.63; N, 16.50; S, 12.69.

Compound ***13db***. IR ($CDCl_3$): 1640 (C=C), 1401 (C=N), 1292 (S–C), 1072 (C–O–C) cm^{-1}. ^1H NMR ($CDCl_3$): δ=1.26 (t, ^3J=7.5 Hz, 3H, CH_2CH_3), 2.13 (d, ^4J=1.2 Hz, 3H, Me-4′), 2.97 (m, 2H, CH_2CH_3, diastereotopic protons), 3.38 (s, 3H, OMe), 3.62 (m, 2H, OCH_2, diastereotopic protons), 5.14 (m, 1H), 5.34 (m, 2H), 6.75 (q, ^4J=1.2 Hz, 1H, H-5′). ^{13}C NMR ($CDCl_3$): δ=11.80 (q, Me), 13.30 (q, Me), 22.29 (t, CH_2CH_3), 59.44 (q, OMe), 75.46 (t, OCH_2), 78.42 (d, C-4), 106.23 (t, $=CH_2$), 115.19 (d, C-5′), 137.21 (s), 147.41 (s), 150.91 (s), 151.65 (s). ESI-MS (m/z) calcd for $C_{12}H_{17}N_3OS$ $[M+H]^+$: 252.1165. Found: 252.1184.

4.8.7. 5-Methyl-2-(4-nitroimidazol-1-yl)thiazole (**12ac**)

Yield: 0.63 g (68%), white solid; mp: 148–150 °C (from diethyl ether). IR ($CDCl_3$): 1554 (C=C), 1517 (NO_2), 1401 (C=N), 1228 (S–C) cm^{-1}. ^1H NMR ($CDCl_3$): δ=2.52 (d, ^4J=1.5 Hz, 3H, Me), 7.32 (q, ^4J=1.5 Hz, 1H, H-4), 8.05 (d, ^4J=1.5 Hz, 1H, H-2′ or H-5′), 8.25 (d, ^4J=1.5 Hz, 1H, H-5′ or H-2′). ^{13}C NMR ($CDCl_3$): δ=12.07 (q, Me), 116.85 (d), 133.56 (s), 133.70 (d), 138.37 (d), 148.62 (s), 152.77 (s). Anal. Calcd for $C_7H_6N_4O_2S$ (242.22): C, 39.99; H, 2.88; N, 26.65; S, 15.25. Found: C, 40.23; H, 2.86; N, 26.58; S, 15.26.

4.8.8. 5-Methyl-2-pyrazol-1-ylthiazole (**12ad**)

Yield: 0.74 g (90%), yellow crystals; mp: 47–48 °C (from diethyl ether). ^1H NMR ($CDCl_3$): δ=2.45 (d, ^4J=1.2 Hz, 3H, CH_3), 6.44 (dd, ^3J=2.61, 1.8 Hz, 1H, =CH), 7.17 (q, ^4J=1.2 Hz, 1H, Th–H-4), 7.68 (dd, ^3J=1.8 Hz, ^4J=0.6 Hz, 1H, =CH), 8.28 (dd, ^3J=2.7 Hz, ^4J=0.6 Hz, 1H, =CH). ^{13}C NMR ($CDCl_3$): δ=12.00 (q, CH_3), 108.32 (d, C=CH), 126.84 (d), 130.62 (s, C-5), 137.06 (d, C=CH), 142.26 (d, C=CH), 159.65 (s, C-2). Anal. Calcd for $C_7H_7N_3S$ (165.22): C, 50.88; H, 4.27; N, 25.43; S, 19.40. Found: C, 50.62; H, 4.02; N, 25.43; S, 19.16.

4.8.9. 5-Ethyl-2-pyrazol-1-ylthiazole (**12bd**) and 5-ethylidene-2-pyrazol-1-yl-4,5-dihydrothiazole (**13bd**)

Following the general procedure, thiazoles **12bd** (0.17 g, 0.950 mmol, 19%) and **13bd** (0.24 g, 1.34 mmol, 27%) were obtained as yellow oils.

Compound ***12bd***. ^1H NMR ($CDCl_3$): δ=1.32 (t, ^3J=7.5 Hz, 3H, CH_3), 2.83 (q, ^3J=7.5 Hz, 2H, CH_2), 6.44 (dd, ^3J=2.7, 1.8 Hz, 1H, =CH), 7.19 (t, ^4J=1.2 Hz, 1H, thiazole =CH), 7.68 (d, ^3J=1.8 Hz, 1H, =CH), 8.27 (dd, ^3J=2.7 Hz, ^4J=0.6 Hz, 1H, =CH). ^{13}C NMR ($CDCl_3$): δ=15.76 (q), 20.52 (t), 108.28 (d), 126.81 (d), 135.42 (d), 138.33 (s), 142.23 (d), 159.43 (s). Anal. Calcd for $C_8H_9N_3S$ (179.24): C, 53.61; H, 5.06; N, 23.44; S, 17.89. Found: C, 53.54; H, 5.11; N, 23.67; S, 17.78.

Compound ***13bd***. ^1H NMR ($CDCl_3$): δ=1.74 (dt, ^3J=6.9 Hz, ^5J=2.4 Hz, 3H, CH_3), 4.96 (m, 2H, CH_2), 5.61 (qt, ^3J=6.6 Hz, ^4J=2.4 Hz, 1H, =CH–CH_3), 6.45 (d, ^3J=2.1 Hz, 1H, =CH), 7.70 (d, ^3J=2.1 Hz, 1H, =CH), 8.28 (t, ^3J=2.1 Hz, 1H, =CH); ^{13}C NMR ($CDCl_3$): δ=17.94 (q), 66.51 (t), 109.68 (d), 114.64 (d), 127.81 (d), 138.03 (s), 142.76 (d), 164.34 (s). ESI-MS (m/z) calcd for $C_8H_9N_3S$ $[M+H]^+$: 180.0590. Found: 180.0648. For the stereochemistry of **13bd**, see the statement on that of **13ba**.

4.8.10. 4,5-Dimethyl-2-pyrazol-1-ylthiazole (**12cd**)

Yield: 0.57 g (77%), white solid; mp: 64–65 °C (from diethyl ether and *n*-hexane). ^1H NMR ($CDCl_3$): δ=2.21 (s, 3H, CH_3), 2.25 (s, 3H, CH_3), 6.35 (dd, ^3J=2.4, 1.2 Hz, 1H, =CH), 7.60 (d, ^3J=1.2 Hz, 1H, =CH), 8.26 (d, ^3J=2.4 Hz, 1H, =CH). ^{13}C NMR ($CDCl_3$): δ=11.20 (q), 14.70 (q), 108.11 (d), 122.85 (s), 126.73 (d), 142.12 (d), 144.99 (s), 156.87 (s). Anal. Calcd for $C_8H_9N_3S$ (179.24): C, 53.61; H, 5.06; N, 23.44; S, 17.89. Found: C, 53.10; H, 5.19; N, 23.19; S, 17.91.

4.8.11. 4-Methoxymethyl-5-methyl-2-pyrazol-1-ylthiazole (**12dd**)

Yield: 0.42 g (91%), pale yellow oil. ^1H NMR ($CDCl_3$): δ=2.44 (s, 3H, CH_3), 3.42 (s, 3H, OCH_3), 4.43 (s, 2H, OCH_2), 6.42 (t, ^3J=2.4 Hz, 1H, =CH), 7.67 (d, ^3J=1.5 Hz, 1H, =CH), 8.31 (d, ^3J=2.4 Hz, 1H, =CH). ^{13}C NMR ($CDCl_3$): δ=11.11 (q), 58.26 (q), 67.42 (t), 108.24 (d), 126.06 (d), 128.45 (s), 142.31 (d), 145.36 (s), 157.76 (s). Anal. Calcd for $C_9H_{11}N_3OS$ (209.27): C, 51.65; H, 5.30; N, 20.08; S, 15.32. Found: C, 51.75; H, 5.53; N, 20.11; S, 15.29.

4.8.12. 2-(3,5-Dimethylpyrazol-1-yl)-5-methylthiazole (**12ae**) and 2-(3,5-dimethylpyrazol-1-yl)-5-methylene-4,5-dihydrothiazole (**13ae**)

Following the general procedure, thiazoles **12ae** (0.50 g, 2.58 mmol, 49%) and **13ae** (0.33 g, 1.70 mmol, 33%) were obtained as yellow oil and white solid (recrystallization from *n*-hexane), respectively.

Compound ***12ae***. IR ($CDCl_3$): 1573 (C=C), 1442 (C=N), 1262 (S–C) cm^{-1}. ^1H NMR ($CDCl_3$): δ=2.26 (s, 3H, Me), 2.41 (d, ^4J=1.2 Hz, 3H, 5-Me), 2.61 (s, 3H, Me), 5.95 (s, 1H, H-4′), 7.13 (q, ^4J=1.2 Hz, 1H, H-4). ^{13}C NMR ($CDCl_3$): δ=11.77 (q, Me), 13.45 (q, Me), 13.50 (q, Me), 109.06 (d, C-4′), 129.78 (s), 137.01 (d, C-4), 141.14 (s), 150.96 (s), 160.56 (s). Anal. Calcd for $C_9H_{11}N_3S$ (193.27): C, 55.93; H, 5.74; N, 21.74. Found: C, 55.77; H, 5.83; N, 21.55.

Compound ***13ae***. Mp: 75–76 °C. IR ($CDCl_3$): 1573 (C=C), 1440 (C=N), 1265 (S–C) cm^{-1}. ^1H NMR ($CDCl_3$): δ=2.23 (s, 3H, Me), 2.53 (s, 3H, Me), 5.02 (t, ^4J=2.7 Hz, 2H, H-4), 5.22 (m, 2H, $=CH_2$), 5.95 (s, 1H, H-4′). ^{13}C NMR ($CDCl_3$): δ=13.52 (q, Me), 13.83 (q, Me), 68.55 (t, C-4), 103.11 (t, $=CH_2$), 110.00 (d, C-4′), 142.55 (s), 146.89 (s), 151.35 (s), 156.69 (s). Anal. Calcd for $C_9H_{11}N_3S$ (193.27): C, 55.93; H, 5.74; N, 21.74; S, 16.59. Found: C, 55.91; H, 5.76; N, 21.58; S, 16.98.

4.8.13. 2-(3,5-Dimethylpyrazol-1-yl)-4-methoxymethyl-5-methylthiazole (**12de**) and 2-(3,5-dimethylpyrazol-1-yl)-4-methoxymethyl-5-methylene-4,5-dihydrothiazole (**13de**)

Following the general procedure, thiazoles **12de** (0.61 g, 2.57 mmol, 50%) and **13de** (0.37 g, 1.56 mmol, 30%) were obtained as colorless oils.

Compound ***12de***. IR ($CDCl_3$): 1573 (C=C), 1412 (C=N), 1365 (S–C), 1083 (C–O–C) cm^{-1}. ^1H NMR ($CDCl_3$): δ=2.25 (s, 3H, Me), 2.42 (s, 3H, Me), 2.63 (s, 3H, Me), 3.41 (s, 3H, OMe), 4.43 (s, 2H, OCH_2), 5.94 (s, 1H, H-4′). ^{13}C NMR ($CDCl_3$): δ=10.44 (q, Me), 13.15 (q, Me), 13.16 (q, Me), 57.70 (q, OMe), 67.30 (t, OCH_2), 108.71 (d, C-4′), 127.44 (s), 140.87 (s), 145.09 (s), 150.54 (s), 158.06 (s). Anal. Calcd for $C_{11}H_{15}N_3OS$ (237.33): C, 55.67; H, 6.37; N, 17.71; S, 13.51. Found: C, 55.47; H, 6.37; N, 17.58; S, 13.68.

Compound ***13de***. IR ($CDCl_3$): 1573 (C=C), 1412 (C=N), 1365 (S–C), 1084 (C–O–C) cm^{-1}. ^1H NMR ($CDCl_3$): δ=2.22 (s, 3H, Me), 2.54 (s, 3H, Me), 3.42 (s, 3H, OMe), 3.62 (m, 2H, OCH_2, diastereotopic protons), 5.19 (m, 1H, CH), 5.31 (m, 2H), 5.94 (s, 1H). ^{13}C NMR ($CDCl_3$): δ=13.50 (q, Me), 13.92 (q, Me), 59.44 (q, OMe), 76.02 (t, OCH_2), 78.75 (d, C-4), 104.81 (t, $=CH_2$), 110.03 (d, C-4′), 142.74 (s), 147.79 (s), 151.47 (s), 156.23 (s). Anal. Calcd for $C_{11}H_{15}N_3OS$ (237.33): C, 55.67; H, 6.37; N, 17.71; S, 13.51. Found: C, 55.37; H, 6.31; N, 17.59; S, 13.91.

*4.8.14. 5-Methyl-2-(3,4,5-trimethylpyrazol-1-yl)thiazole (**12af**) and 5-methylene-2-(3,4,5-trimethylpyrazol-1-yl)-4,5-dihydrothiazole (**13af**)*

Following the general procedure, thiazoles **12af** (0.62 g, 3.00 mmol, 66%) and **13af** (0.21 g, 1.00 mmol, 22%) were obtained as white solids (recrystallization from *n*-hexane).

*Compound **12af***. Mp: 82–83 °C. IR ($CDCl_3$): 1595 (C=C), 1449 (C=N), 1277 (S–C) cm^{-1}. ^1H NMR ($CDCl_3$): δ=1.94 (s, 3H, Me), 2.21 (s, 3H, Me), 2.40 (d, ^4J=1.3 Hz, 3H, Me), 2.55 (s, 3H, Me), 7.12 (q, ^4J=1.3 Hz, 1H, H-4). ^{13}C NMR ($CDCl_3$): δ=7.81 (q, Me), 11.77 (q, Me), 11.81 (q, Me), 12.02 (q, Me), 115.46 (s), 129.29 (s), 136.87 (d, C-4), 137.45 (s), 150.57 (s), 161.01 (s). Anal. Calcd for $C_{10}H_{13}N_3S$ (207.29): C, 57.94; H, 6.32; N, 20.27; S, 15.47. Found: C, 57.73; H, 6.35; N, 19.96; S, 16.02.

*Compound **13af***. Mp: 72–73 °C. IR ($CDCl_3$): 1619 (C=C), 1432 (C=N), 1275 (S–C) cm^{-1}. ^1H NMR ($CDCl_3$): δ=1.91 (s, 3H, Me), 2.18 (s, 3H, Me), 2.46 (s, 3H, Me), 5.01 (t, ^4J=2.4 Hz, 2H), 5.21 (t, ^4J=2.4 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ=7.73 (q, Me), 12.05 (q, Me), 12.10 (q, Me), 68.49 (t, C-4), 102.86 (t, =CH_2), 116.44 (s), 138.51 (s), 146.89 (s), 151.16 (s), 156.85 (s). Anal. Calcd for $C_{10}H_{13}N_3S$ (207.29): C, 57.94; H, 6.32; N, 20.27; S, 15.47. Found: C, 57.93; H, 6.25; N, 20.22; S, 15.59.

*4.8.15. 4-Methoxymethyl-5-methyl-2-(3,4,5-trimethylpyrazol-1-yl)thiazole (**12df**) and 4-methoxymethyl-5-methylene-2-(3,4,5-trimethylpyrazol-1-yl)-4,5-dihydrothiazole (**13df**)*

Following the general procedure, thiazoles **12df** (0.44 g, 1.75 mmol, 39%) and **13df** (0.52 g, 2.07 mmol, 46%) were obtained as white solid (recrystallization from *n*-hexane) and colorless oil, respectively.

*Compound **12df***. Mp: 79–80 °C. IR ($CDCl_3$): 1595 (C=C), 1431 (C=N), 1363 (S–C), 1084 (C–O–C) cm^{-1}. ^1H NMR ($CDCl_3$): δ=1.89 (s, 3H, Me), 2.17 (s, 3H, Me), 2.37 (s, 3H, Me), 2.53 (s, 3H, Me), 3.38 (s, 3H, OMe), 4.39 (s, 2H, OCH_2). ^{13}C NMR ($CDCl_3$): δ=7.67 (q, Me), 10.70 (q, Me), 11.67 (q, Me), 11.89 (q, Me), 57.94 (q, OMe), 67.55 (t, OCH_2), 115.26 (s), 127.18 (s), 137.39 (s), 145.08 (s), 150.40 (s), 158.68 (s). Anal. Calcd for $C_{12}H_{17}N_3OS$ (251.35): C, 57.19; H, 6.83; N, 16.76; S, 13.03. Found: C, 57.16; H, 6.66; N, 16.81; S, 12.85.

*Compound **13df***. IR ($CDCl_3$): 1638 (C=C), 1431 (C=N), 1363 (S–C), 1120 (C–O–C) cm^{-1}. ^1H NMR ($CDCl_3$): δ=1.84 (s, 3H, Me), 2.11 (s, 3H, Me), 2.42 (s, 3H, Me), 3.37 (s, 3H, OMe), 3.50 (m, 2H, OCH_2, diastereotopic protons), 5.12 (m, 1H), 5.24 (m, 2H). ^{13}C NMR ($CDCl_3$): δ=7.42 (q, Me), 11.74 (q, Me), 11.94 (q, Me), 59.15 (q, OMe), 75.91 (t, OCH_2), 78.41 (d, C-4), 104.28 (t, =CH_2), 116.23 (s), 138.37 (s), 147.70 (s), 150.94 (s), 156.12 (s). Anal. Calcd for $C_{12}H_{17}N_3OS$ (251.35): C, 57.19; H, 6.83; N, 16.76; S, 13.03. Found: C, 57.34; H, 6.82; N, 16.72; S, 12.67.

*4.8.16. 2-[1-(5-Methylthiazol-2-yl)-1H-pyrazol-3-yl]-pyridine (**12ag**)*

Yield: 0.45 g (91%), white solid; mp: 124–125 °C (from diethyl ether). IR ($CDCl_3$): 1550 (C=C), 1422 (C=N), 1261 (S–C) cm^{-1}. ^1H NMR ($CDCl_3$): δ=2.45 (d, ^4J=1.3 Hz, 3H, Me), 7.10 (d, ^3J=3.0 Hz, 1H, H-4′), 7.18 (q, ^4J=1.3 Hz, 1H, H-4″), 7.24 (ddd, ^3J=7.5, 4.8 Hz, ^4J=1.2 Hz, 1H, H-5), 7.74 (ddd, ^3J=7.8, 7.5 Hz, ^4J=1.7 Hz, 1H, H-4), 8.07 (ddd, ^3J=7.8 Hz, ^4J=1.2 Hz, ^5J=1.0 Hz, 1H, H-3), 8.31 (d, ^3J=3.0 Hz, 1H, H-5′), 8.64 (ddd, ^3J=4.8 Hz, ^4J=1.7 Hz, ^5J=1.0 Hz, 1H, H-6). ^{13}C NMR ($CDCl_3$): δ=11.99 (q, 5″-Me), 107.14 (d, C-4′), 120.51 (d, C-3), 123.13 (d, C-5), 128.22 (d, C-5′), 130.79 (s, C-5″), 136.57 (d, C-4), 137.17 (d, C-4″), 149.40 (d, C-6), 151.00 (s), 154.21 (s), 159.43 (s), assignments by C–H shift correlation. Anal. Calcd for $C_{12}H_{10}N_4S$ (242.30): C, 59.48; H, 4.14; N, 22.93; S, 13.38. Found: C, 59.15; H, 4.15; N, 23.12; S, 13.23.

*4.8.17. 2-[1-(4-Methoxymethyl-5-methylthiazol-2-yl)-1H-pyrazol-3-yl]pyridine (**12dg**)*

Yield: 0.52 g (88%), white solid; mp: 108–109 °C (from *n*-hexane). IR ($CDCl_3$): 1545 (C=C), 1404 (C=N), 1366 (S–C), 1086 (C–O–C) cm^{-1}. ^1H NMR ($CDCl_3$): δ=2.46 (s, 3H, Me), 3.44 (s, 3H, OMe), 4.44 (s, 2H, OCH_2), 7.10 (d, ^3J=2.6 Hz, 1H, H-4′), 7.25 (ddd, ^3J=7.7, 4.9 Hz, ^4J=1.3 Hz, 1H, H-5), 7.75 (ddd, ^3J=7.9, 7.7 Hz, ^4J=1.9 Hz, 1H, H-4), 8.06 (ddd, ^3J=7.9 Hz, ^4J=1.3 Hz, ^5J=1.0 Hz, 1H, H-3), 8.36 (d, ^3J=2.6 Hz, 1H, H-5′), 8.64 (ddd, ^3J=4.9 Hz, ^4J=1.9 Hz, ^5J=1.0 Hz, 1H, H-6). ^{13}C NMR ($CDCl_3$): δ=11.14 (q, 5″-Me), 58.31 (q, OMe), 67.43 (t, OCH_2), 107.12 (d, C-4′), 120.56 (d, C-3), 123.16 (d, C-5), 128.48 (d, C-5′), 128.68 (s), 136.64 (d, C-4), 145.47 (s), 149.37 (d, C-6), 150.96 (s), 154.20 (s), 157.58 (s), assignments by C–H shift correlation. Anal. Calcd for $C_{14}H_{14}N_4OS$ (286.36): C, 58.72; H, 4.93; N, 19.57; S, 11.20. Found: C, 58.49; H, 4.90; N, 19.42; S, 11.31.

*4.8.18. 1-(5-Methylthiazol-2-yl)-1H-benzimidazole (**12ah**)*

Yield: 0.64 g (85%), brown crystals; mp: 88–90 °C (from acetone). ^1H NMR ($CDCl_3$): δ=2.44 (d, ^4J=1.2 Hz, 3H, CH_3), 7.33 (q, ^4J=1.2 Hz, 1H, H-4′), 7.35 (t, ^3J=7.5 Hz, 2H, 2×=CH), 7.81 (d, ^3J=7.5 Hz, 1H, =CH), 7.97 (d, ^3J=7.5 Hz, 1H, =CH), 8.43 (s, 1H, H-2). ^{13}C NMR ($CDCl_3$): δ=11.81 (q, CH_3), 112.06 (d), 120.62 (d, C=CH), 123.70 (d, C=CH), 124.63 (d, C=CH), 130.17 (s), 131.59 (s), 137.29 (d, C=CH), 140.81 (d, C=CH), 143.83 (s, C=C), 154.73 (s, C-2′). Anal. Calcd for $C_{11}H_9N_3S$ (215.28): C, 61.37; H, 4.21; N, 19.51; S, 14.90. Found: C, 61.23; H, 4.05; N, 19.41; S, 15.39.

*4.8.19. 1-(5-Methylthiazol-2-yl)-1H-benzimidazol-2-ylamine (**12ai**)*

Yield: 0.34 g (83%), yellow crystals; mp: 173–175 °C (from diethyl ether). ^1H NMR (DMSO-d_6): δ=2.53 (d, ^4J=1.2 Hz, 3H, CH_3), 7.02 (t, ^3J=6.6 Hz, 1H, =CH), 7.12 (t, ^3J=6.6 Hz, 1H, =CH), 7.24 (d, ^3J=6.6 Hz, 1H, =CH), 7.35 (br, 2H, NH_2), 7.45 (q, ^4J=1.2 Hz, 1H, H-4′), 7.49 (d, ^3J=6.6 Hz, 1H, =CH). ^{13}C NMR (DMSO-d_6): δ=11.54 (q, CH_3), 109.33 (d, =CH), 115.83 (d, =CH), 119.68 (d, =CH), 123.24 (d, =CH), 130.34 (s, C=C), 131.36 (s, C=C), 136.63 (d, =CH), 142.95 (s, C=C), 153.37 (s), 155.35 (s). Anal. Calcd for $C_{11}H_{10}N_4S$ (230.22): C, 57.38; H, 4.34; N, 24.33; S, 13.93. Found: C, 56.94; H, 4.30; N, 24.25; S, 14.00.

*4.8.20. 2-Ethyl-1-(5-methylthiazol-2-yl)-1H-benzimidazole (**12aj**)*

Yield: 1.00 g (82%), yellow crystals; mp: 56–57 °C (from acetone). ^1H NMR ($CDCl_3$): δ=1.40 (t, ^3J=7.8 Hz, 3H, CH_3), 2.57 (d, ^4J=1.2 Hz, 3H, CH_3 at C-5′), 3.07 (q, ^3J=7.8 Hz, 2H, CH_2), 7.29 (t, ^3J=5.8 Hz, 2H, 2×=CH), 7.46 (q, ^4J=1.2 Hz, 1H, H-4′), 7.53 (d, ^3J=5.8 Hz, 1H, =CH), 7.77 (d, ^3J=5.8 Hz, 1H, =CH). ^{13}C NMR ($CDCl_3$): δ=11.62 (q, CH_3), 12.24 (q, CH_3), 21.88 (t, ethyl CH_2), 110.46 (d, C=CH), 119.34 (d, C=CH), 123.25 (d, C=CH), 123.42 (d, C=CH), 134.48 (s, C=C), 135.40 (s, C=C), 138.23 (d, C=CH), 142.25 (s, C=C), 153.85 (s), 156.29 (s). Anal. Calcd for $C_{13}H_{13}N_3S$ (207.30): C, 64.16; H, 5.38; N, 17.26; S, 13.28. Found: C, 63.70; H, 5.41; N, 17.20; S, 13.64.

*4.8.21. 2-Ethyl-1-(4-methoxymethyl-5-methylthiazol-2-yl)-1H-benzimidazole (**12dj**) and 2-ethyl-1-(4-methoxymethyl-5-methylene-4,5-dihydrothiazol-2-yl)-1H-benzimidazole (**13dj**)*

Following the general procedure, thiazoles **12dj** (0.60 g, 2.09 mmol, 76%) and **13dj** (0.13 g, 0.45 mmol, 17%) were obtained as yellow oils.

*Compound **12dj***. IR ($CDCl_3$): 1613 (C=C), 1453 (C=N), 1364 (S–C), 1075 (C–O–C) cm^{-1}. ^1H NMR ($CDCl_3$): δ=1.30 (t, ^3J=7.8 Hz, 3H, CH_2CH_3), 2.39 (s, 3H, Me-5′), 2.95 (q, ^3J=7.8 Hz, 2H, CH_2CH_3), 3.32 (s, 3H, OMe), 4.41 (s, 2H, OCH_2), 7.14 (m, 2H, 2×Ar–H), 7.45 (m, 1H, Ar–H), 7.64 (m, 1H, Ar–H). ^{13}C NMR ($CDCl_3$): δ=10.86 (q, Me), 11.20 (q, Me), 21.56 (t, CH_2CH_3), 57.96 (q, OMe), 67.05 (t, OCH_2), 110.19 (d), 118.94 (d), 122.80 (d), 123.00 (d), 131.86 (s), 134.72 (s), 141.95 (s), 146.30 (s), 151.45 (s), 155.78 (s). Anal. Calcd for $C_{15}H_{17}N_3OS$ (287.38): C, 62.69; H, 5.96; N, 14.62; S, 11.16. Found: C, 62.50; H, 5.78; N, 14.60; S, 11.62.

*Compound **13dj***. IR ($CDCl_3$): 1615 (C=C), 1456 (C=N), 1364 (S–C), 1073 (C–O–C) cm^{-1}. ^1H NMR ($CDCl_3$): δ=1.43 (t, ^3J=7.8 Hz, 3H,

CH_2Me), 3.14 (m, 2H, CH_2Me, diastereotopic protons), 3.41 (s, 3H, OMe), 3.75 (m, 2H, OCH_2, diastereotopic protons), 5.27 (m, 1H, H-4′), 5.41 (dd, ^4J=2.5 Hz, ^2J=2.1 Hz, 1H, C=CH_2), 5.47 (dd, ^4J=2.3 Hz, ^2J=2.1 Hz, 1H, C=CH_2), 7.27 (m, 2H, 2×Ar–H), 7.72 (m, 2H, 2×Ar–H). ^{13}C NMR ($CDCl_3$): δ=11.61 (q, CH_2Me), 22.59 (t, CH_2Me), 59.30 (q, OMe), 75.31 (t, OCH_2), 77.14 (d, C-4′), 106.54 (t, =CH_2), 112.10 (d), 119.29 (d), 123.41 (d, 2×Ar–C), 133.82 (s), 142.14 (s), 147.31 (s), 152.22 (s), 156.08 (s). Anal. Calcd for $C_{15}H_{17}N_3OS$ (287.38): C, 62.69; H, 5.96; N, 14.62; S, 11.16. Found: C, 62.14; H, 6.04; N, 14.67; S, 11.52.

*4.8.22. 1-(5-Methylthiazol-2-yl)-1H-indazole (**12ak**)*

Yield: 0.78 g (95%), white solid; mp: 138–140 °C (from diethyl ether and *n*-hexane). ^{1}H NMR ($CDCl_3$): δ=2.46 (d, ^4J=1.2 Hz, 3H, CH_3), 7.10 (d, ^3J=7.5 Hz, 1H, aromatic =CH), 7.30 (q, ^4J=1.2 Hz, 1H, thiazole =CH), 7.33 (d, ^3J=7.5 Hz, 1H, aromatic =CH), 7.69 (t, ^3J=7.5 Hz, 2H, two aromatic =CH), 8.78 (d, ^4J=1.2 Hz, 1H, pyrazole =CH). ^{13}C NMR ($CDCl_3$): δ=12.00 (q), 117.69 (d), 119.95 (d), 120.81 (d), 122.33 (s), 123.17 (d), 127.92 (d), 132.64 (s), 137.78 (d), 150.04 (s), 159.64 (s). Anal. Calcd for $C_{11}H_9N_3S$ (215.28): C, 61.37; H, 4.21; N, 19.51; S, 14.90. Found: C, 61.43; H, 4.20; N, 19.08; S, 14.51.

*4.8.23. 1-(5-Methylthiazol-2-yl)-1H-1,2,3-triazole (**12al**)*

Yield: 0.57 g (69%), yellow crystals; mp: 45–47 °C (from acetone). ^{1}H NMR ($CDCl_3$): δ=2.51 (d, ^4J=1.2 Hz, 3H, CH_3), 7.32 (q, ^4J=1.2 Hz, 1H, H-4′), 7.38 (d, ^3J=1.2 Hz, 1H, =CH), 7.81 (d, ^3J=1.2 Hz, 1H, =CH). ^{13}C NMR ($CDCl_3$): δ=11.72 (q, CH_3), 120.94 (d), 132.94 (s, C-5′), 134.06 (d), 137.31 (d), 154.77 (s, C-2′). Anal. Calcd for $C_6H_6N_4S$ (166.21): C, 43.35; H, 3.63; N, 33.70; S, 19.29. Found: C, 43.49; H, 3.34; N, 33.35; S, 19.49.

*4.8.24. 1-(5-Methylthiazol-2-yl)-1H-benzotriazole (**12am**)*

Yield: 0.93 g (86%), yellow crystals; mp: 105–106 °C (from acetone). ^{1}H NMR ($CDCl_3$): δ=2.52 (d, ^4J=1.2 Hz, 3H, CH_3), 7.38 (q, ^4J=1.2 Hz, 1H, H-4′), 7.47 (t, ^3J=7.2 Hz, 1H, =CH), 7.63 (t, ^3J=7.2 Hz, 1H, =CH), 8.10 (d, ^3J=7.2 Hz, 1H, =CH), 8.43 (d, ^3J=7.2 Hz, 1H, =CH). ^{13}C NMR ($CDCl_3$): δ=11.96 (q, CH_3), 113.36 (d, C-4′), 119.99 (d, C=CH), 125.48 (d, C=CH), 129.48 (d, C=CH), 130.84 (s), 131.24 (s), 137.69 (d, C=CH), 146.37 (s), 159.65 (s). Anal. Calcd for $C_{10}H_8N_4S$ (216.27): C, 55.53; H, 3.72; N, 25.90; S, 14.82. Found: C, 55.41; H, 3.71; N, 25.78; S, 15.09.

*4.8.25. 4-(5-Methylthiazol-2-yl)-4H-1,2,4-triazole (**12an**) and 1-(5-methylthiazol-2-yl)-1H-1,2,4-triazole (**12an′**)*

Following the general procedure, thiazoles **12an** (0.53 g, 64%) and **12an′** (0.22 g, 26%) were obtained as yellow solids. Each product was recrystallized from acetone.

*Compound **12an***. Mp: 105–107 °C. ^{1}H NMR ($CDCl_3$): δ=2.52 (d, ^4J=1.2 Hz, 3H, CH_3), 7.31 (q, ^4J=1.2 Hz, 1H, H-4′), 8.67 (s, 2H, H-3, H-5). ^{13}C NMR ($CDCl_3$): δ=12.05 (q, CH_3), 132.93 (d, C-4′), 138.19 (s, C-5′), 140.20 (d, C-3, C-5), 151.31 (s, C-2′). Anal. Calcd for $C_6H_6N_4S$ (166.21): C, 43.62; H, 3.05; N, 33.91; S, 19.53. Found: C, 43.39; H, 3.42; N, 33.49; S, 19.41.

*Compound **12an′***. Mp: 93–94 °C. ^{1}H NMR ($CDCl_3$): δ=2.49 (d, ^4J=1.2 Hz, 3H, CH_3), 7.26 (q, ^4J=1.2 Hz, 1H, H-4′), 8.04 (s, 1H, =CH), 8.91 (s, 1H, =CH). ^{13}C NMR ($CDCl_3$): δ=11.94 (q, CH_3), 132.65 (d), 137.62 (d), 140.60 (d), 143.89 (s), 152.63 (s). Anal. Calcd for $C_6H_6N_4S$ (166.21): C, 43.62; H, 3.05; N, 33.91; S, 19.53. Found: C, 43.28; H, 3.55; N, 33.75; S, 18.65.

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