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REGIO- AND STEREOSELECTIVE SYNTHESIS OF THIAZOLE-SUBSTITUTED HISTAMINE AND ADENINE DERIVATIVES BY NUCLEOPHILIC ATTACK AT ALLENYL ISOTHIOCYANATE†

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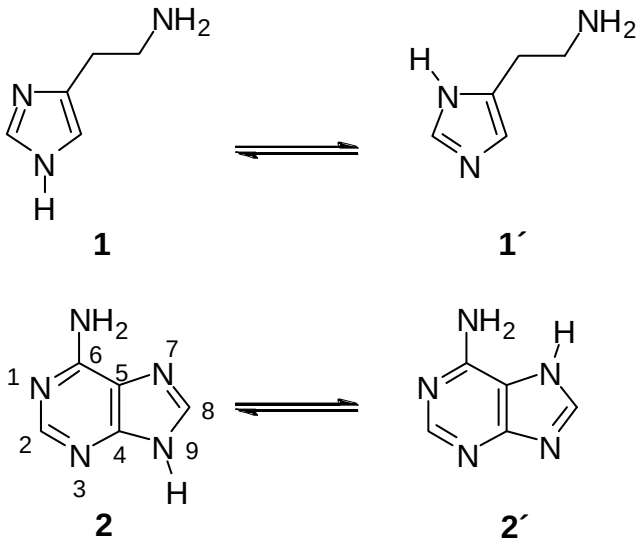
Abstract – The ambident oligonucleophiles histamine and adenine were reacted with allenyl isothiocyanate to yield *N*-(5-methylthiazol-2-yl) substituted derivatives of the natural products. Whereas histamine led selectively in three clean steps or alternatively in a one-pot procedure to a final product bearing three thiazole units, adenine gave exclusively the mono derivative with a thiazolyl group at N-7. The regio- and stereochemistry of these transformations were proved by single-crystal X-ray analyses of the title compounds.

INTRODUCTION

Histamine (**1**) is a naturally occurring compound, which is an important mediator of inflammation and gastric acid secretion (Scheme 1).[1] It has two interesting nucleophilic moieties, the imidazole ring and the primary amino group. Because of the tautomeric forms of **1**, both nitrogen atoms of the imidazole unit can function as a nucleophilic center. The nucleophilicity of **1** was studied using kinetic investigations.[2]

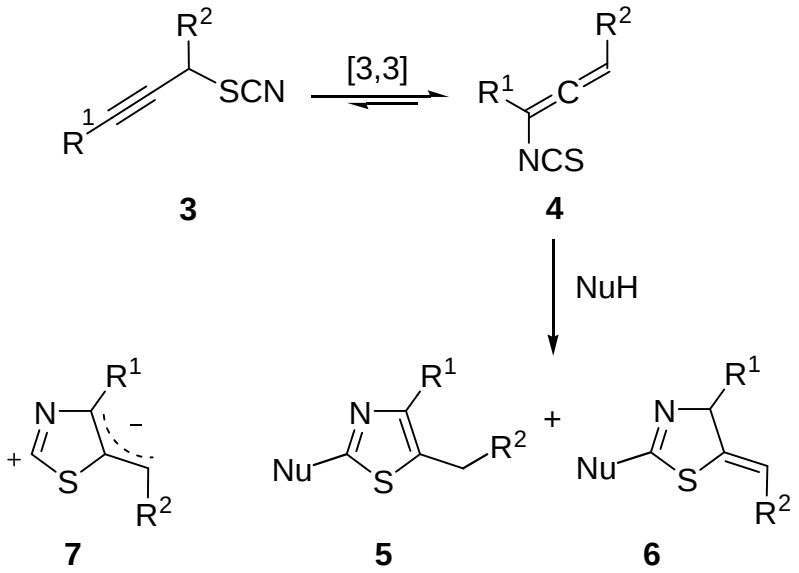


Scheme 1. Tautomeric structures of histamine (**1**) and adenine (2)

Adenine (**2**), which exists in many biological systems, for example, as a basic part of RNA and DNA (Scheme 1),[3] is also a naturally occurring oligonucleophile with different tautomeric forms. The stability order for N-substituted adenines was investigated by tautomeric equilibria studies,[4] alkyl rearrangement reactions,[5] and self-consistent field (SCF) molecular orbital calculations.[6] Moreover, the determining factor for the relative reaction rates of heterocyclic nitrogen is governed by the steric factor.[7] Although the reaction at N-9[8] is usually dominant, there have been many reports of minor nucleophilic attack by N-3[9] and/or N-7.[10] The nucleophilicity of adenine in native and denatured DNA was analysed quantitatively.[11]

The electrophilic reagent, which will be used to execute this study, is the highly reactive 1-isothiocyanatopropa-1,2-diene (**4a**). Allenyl isothiocyanates of type **4** can be easily generated via the thermal [3,3]-sigmatropic rearrangement of propargyl thiocyanates **3** using flash vacuum pyrolysis (Scheme 2).[12] Cumulenes **4** are known to yield thiazoles **5** and **6**, when they are treated with carbon-, oxygen-, nitrogen-, phosphorus-, sulfur-, or hydride-containing nucleophiles NuH. Thus, the chemistry of **4** illustrates that allenyl isothiocyanates act predominantly as synthetic equivalents of synthons **7**.[13]

We report now on the reactions of the isothiocyanate **4a** with histamine (**1**) and adenine (**2**), respectively, to reveal selectively thiazole[14] derivatives of type **5**.



Scheme 2. Generation of allenyl isothiocyanates **4** and their transformation into thiazole derivatives

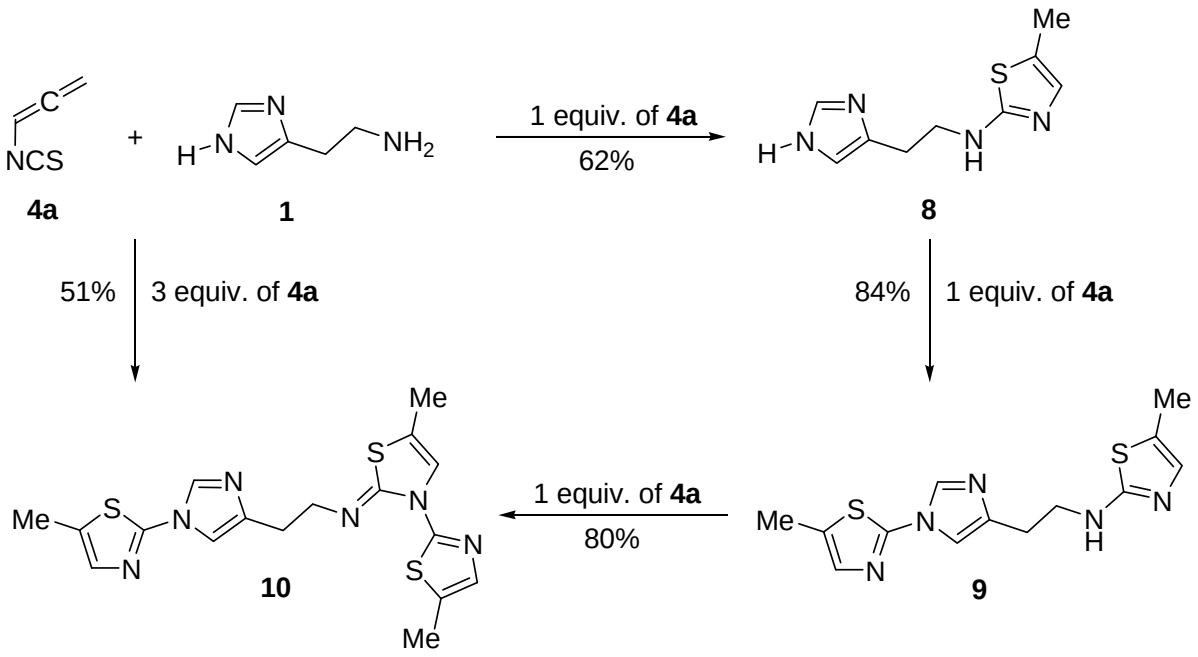
RESULTS AND DISCUSSION

Reaction of Allenyl Isothiocyanate (4a) with Histamine (1)

To investigate the reactivity of histamine (**1**), it was treated step by step with a threefold molar excess of allene **4a** (Scheme 3). Using the ^{1}H NMR chemical shifts of the starting material **1** in CD_3OD as a reference, we noticed a clear downfield shift for the signals of four protons of the ethano chain (2.86 and 3.47 ppm) of product **8**,[15] whereas the signals of the imidazole unit (6.84 and 7.57 ppm) remained nearly unchanged. In the starting material **1**, the corresponding signals were found at δ = 2.71, 2.85, 6.80, and 7.54. The downfield shift of the signals of compound **8** was caused by the formation of the thiazole ring on the amino group. The nucleophilicity of the primary amino group was obviously stronger than that of the imidazole moiety.[16] Additionally, the IR spectrum of thiazole **8**, which was isolated in 62% yield, revealed two typical amino bands at 3447 cm^{-1} (NH of the imidazole ring) and 3218 cm^{-1} (NH of the secondary amine). Since the absorption bands of the primary amine (NH_2) and imidazole moiety of the starting material **1** appeared as a broad band (2700–3500 cm^{-1}), it was nearly impossible to include them in comparison studies of IR results for this reaction.

When **8** was treated with another equivalent of **4a**, product **9** was obtained in 84% yield. On the basis of the ^{1}H NMR spectrum, the chemical shifts of the imidazole protons of **9** (7.46 and 8.22 ppm in CD_3OD), which had been shifted downfield in comparison to the corresponding signals of the starting material **8** (6.84 and 7.57 ppm in CD_3OD), proved clearly the formation of a thiazole ring adjacent to the imidazole moiety. On the other hand, the four protons of the ethano chain of compound **9** revealed only a small difference in their

^{1}H NMR chemical shifts compared to those of molecule **8**. The absence of the absorption band at 3447 cm^{-1} (NH of the imidazole moiety) and the presence of the characteristic absorption band at 3195 cm^{-1} (NH of the secondary aromatic amine), in comparison with the IR spectrum of thiazole **8**, were additional proofs of the expected structure of histamine derivative **9**. The nucleophilic attack occurred from the imidazole moiety rather than from the secondary amine due to the steric factor and the low nucleophilicity of this amine.



Scheme 3. Reaction of histamine (**1**) with allenyl isothiocyanate (**4a**)

Finally, subjecting compound **9** with one equivalent of allene **4a** gave the product **10** in 80% yield. On the other hand, treating histamine (**1**) with an excess of allene **4a** in a one-pot reaction afforded the tris-thiazole derivative **10** with a yield of 51%. The regiochemistry and the stereochemistry of this transformation was investigated by a single-crystal X-ray analysis of the final product **10** (Figure 1, Table 1). Obviously, the thiazole ring was regioselectively formed at the less sterically hindered nitrogen of the imidazole moiety. The stereochemistry of the imino group was found to exhibit (*Z*) configuration, which can be explained by steric effects.

Compound **10** forms in the solid state 2D-layers due to intermolecular π-π interactions. A selected view of a part of one 2D-layer is shown in Figure 2, giving geometrical details.

Reaction of Allenyl Isothiocyanate (4a) with Adenine (2)

Adenine (**2**) was treated with an excess amount of the allenyl isothiocyanate (**4a**) in order to investigate the reactivities of the N-1, N-3, N-7, N-9, and the primary aromatic amine (NH_2) (Scheme 4). We expected the

formation of a polysubstituted adenine derivative. Surprisingly, we isolated only the monosubstituted adenine **11** in 42% yield.[17] This product was regioselectively formed by attack of the more sterically

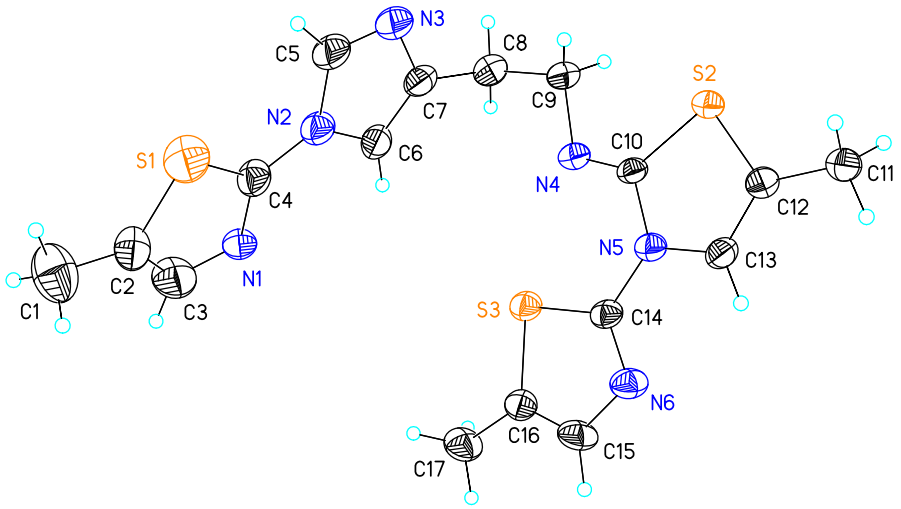


Figure 1. ORTEP (30% probability level) of the molecular structure of **10**

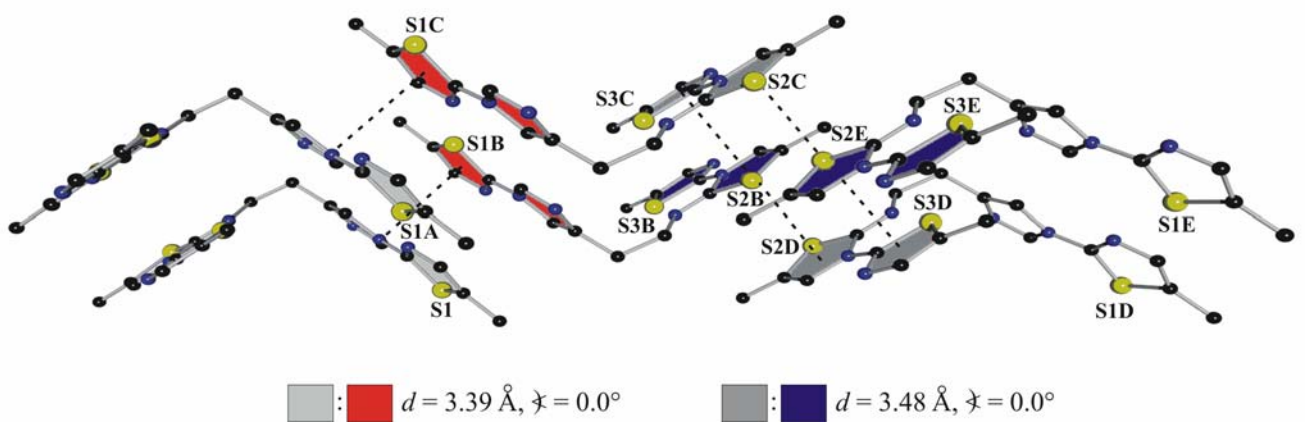
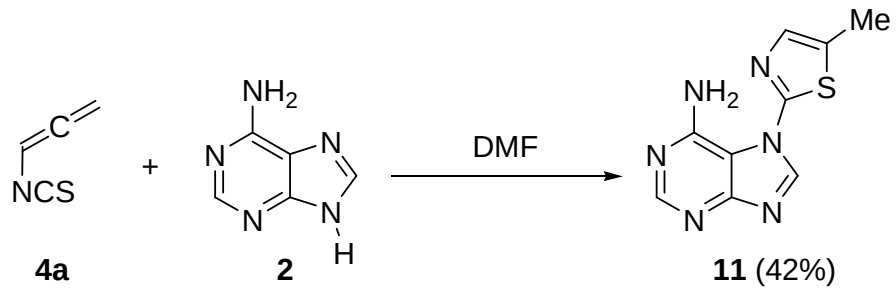


Figure 2. Part of the 2D-layer of **10** formed in the solid state due to π-π interactions, with *d* giving distances of calculated mean planes of interacting 2-(1*H*-imidazole-1-yl)thiazole and 2,3'-bithiazolyl units, respectively (∢ stands for the interplanar angles)

hindered and less nucleophilic nitrogen N-7. The IR spectrum of thiazole **11** showed only the absorption band of the primary aromatic amino group (NH_2) at 3254 cm^{-1}. The structure of compound **11** was confirmed by single-crystal X-ray study as shown in Figure 3. Crystals of adenine derivative **11** were obtained as beige plates from a solution in methanol at 25 °C. These crystals were monoclinic, $P2_1/n$, and contain four molecules within the unit cell. Molecules of **11** crystallizes in form of a centrosymmetric hydrogen-bridged dimer, held together by mutual, intermolecular NH---N bridges with *d*[(N(10)–H4---N(1A)] = 3.041(6) Å. A further, intramolecular N–H---N hydrogen bond with

d[(N(10)–H3---N(11)] = 2.790(6) Å is observed, considerably stronger compared to the intermolecular interaction.[18] Finally, two MeOH molecules are bound to the dimer of **11**, due to the formation of an OH---N hydrogen bond with *d*[O(1)–H9---N(3)] = 2.808(5) Å (Figure 3 and Table 2). Furthermore, compound **11** forms in the solid state 2D-layers due to intermolecular π-π interactions. A view of a selected part of one 2D-layer is given in Figure 4.

The unusual formation of product **11** from **2** and **4a** can be explained by postulating a hydrogen bonding association between the 6-amino group (N-10) and the partially negatively charged nitrogen atom of the isothiocyanato group in the transition state leading to **11**. Most probably, **11** does not react with another molecule of **4a** due to steric hindrance and the internal hydrogen bonding between the amino group and the thiazole nitrogen as strongly indicated in the X-ray structure.



Scheme 4. Synthesis of adenine derivative **11**

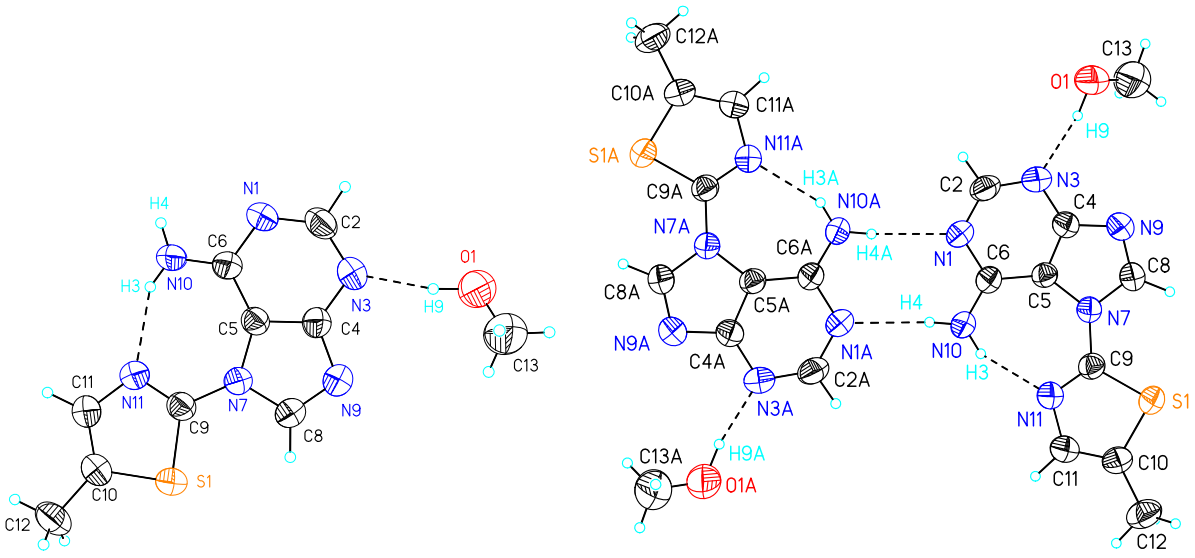


Figure 3. ORTEP (50% probability level) of the molecular structure of the asymmetric unit of 11·MeOH (left) and the associate $\{11\cdot MeOH\}_2$ (right) formed by intermolecular hydrogen bonds

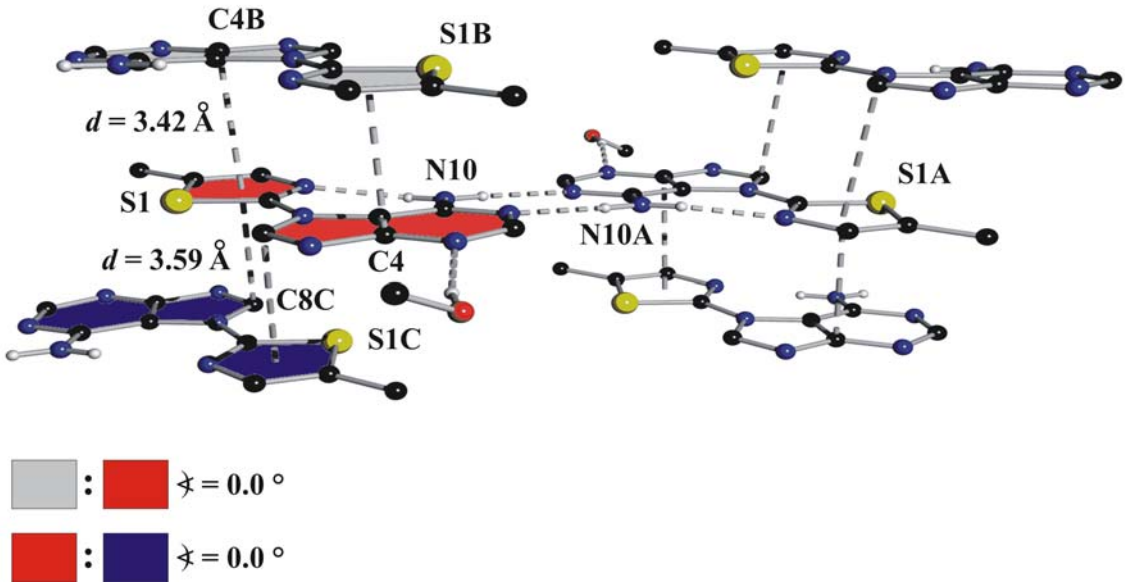


Figure 4. Part of the 2D-layer of 11 formed in the solid state due to π-π interactions, with *d* giving the shortest distances of labeled carbon atoms with calculated centroids of five-membered aromatic rings (∢ stands for the interplanar angles)

CONCLUSIONS

On the one hand, treatment of cumulene **4a** with histamine (**1**) indicated that the latter is a triple nucleophile with well graded reactivity. The primary amino group of **1** shows a higher nucleophilicity than the imidazole unit. But this heterocycle is more reactive than the 2-aminothiazole moiety generated in the first step. The regioselectivity of the nucleophilic attack of intermediate **8** at **4a** and the stereochemistry of the final product **10** are easily interpreted by steric factors. On the other hand, subjection of adenine (**2**) to an excess of **4a** yielded exclusively the mono-thiazole derivative **11** after attack of the more sterically hindered and less nucleophilic nitrogen N-7. This unusual result can be explained due to hydrogen bonding association between the primary amino group at C-6 and the nitrogen atom of **4a** in the transition state leading to **11**.

EXPERIMENTAL

General: ^{1}H NMR spectra were recorded at 300 MHz, ^{13}C NMR spectra at 75 MHz. Chemical shifts (δ) are reported in parts per million (ppm) downfield from TMS or recalculated from solvent signals. The spin multiplicities of the ^{13}C NMR signals were obtained by DEPT experiments. Infrared spectra were recorded as solids in KBr disc. TLC was performed on Macherey-Nagel precoated silica gel Polygram Sil G/UV$_{254}$ plates and viewed by UV. Chromatography refers to flash chromatography,[19] carried out on Fluka silica gel 60. For the elemental analyses, Vario El (Elementar Analysensysteme GmbH) was employed.

Warning: In the case of unstable compound **4a**, it was useful to minimize polymerization by dilution of the collected substance with a weighed quantity of an inert solvent before thawing the trap of the apparatus

used for flash vacuum pyrolysis.[13] Otherwise, a dangerously vigorous reaction is possible since at room temperature undiluted allenyl isothiocyanate (**4a**) tends to spontaneous and very exothermic polymerization.

Synthesis of [2-(1*H*-Imidazol-4-yl)ethyl]-(5-methylthiazol-2-yl)amine (8):

1-Isothiocyanatopropa-1,2-diene (**4a**)[13] 10% in dry DMF (0.26 g, 2.70 mmol) was added dropwise to 2-(1*H*-imidazol-4-yl)ethylamine (**1**) (0.30 g, 2.70 mmol) in dry DMF (10 mL). After stirring for 30 min at rt, the solvent was removed in vacuo, and the crude compound was isolated by flash chromatography utilizing MeOH/EtOAc (4:6) to give [2-(1*H*-imidazol-4-yl)ethyl]-(5-methylthiazol-2-yl)amine (**8**) as a white solid (0.35 g, 1.68 mmol, 62%). Recrystallization was performed from MeOH and EtOAc, mp 156–157 °C. IR (KBr): $\tilde{\nu}$ = 3447 (NH), 3218 (NH), 1591, 1451, 1135 cm^{-1}; ^1H NMR (300 MHz, CD_3OD): δ = 2.20 (d, ^4J = 1.5 Hz, 3 H, Me), 2.86 (t, J = 7.2 Hz, 2 H, CH_2), 3.47 (t, J = 7.2 Hz, 2 H, NCH_2), 6.62 (q, ^4J = 1.5 Hz, 1 H, =CH), 6.84 (dt, ^4J = 1.2 Hz, ^4J = 0.9 Hz, 1 H, =CH), 7.57 (d, ^4J = 1.2 Hz, 1 H, =CH); ^{13}C NMR (75 MHz, CD_3OD): δ = 11.76 (q, Me), 27.56 (t, C-2), 45.65 (t, C-1), 118.19 (d), 121.35 (s), 135.31 (d), 135.69 (s), 135.93 (d), 170.64 (s). Anal. Calcd for $C_9H_{12}N_4S$ (208.15): C 51.90, H 5.81, N 26.90, S 15.40. Found: C 51.51, H 5.98, N 26.73, S 15.86.

Synthesis of (5-Methylthiazol-2-yl)-{2-[1-(5-methylthiazol-2-yl)-1*H*-imidazol-4-yl]ethyl}amine (9):

1-Isothiocyanatopropa-1,2-diene (**4a**) 10% in dry DMF (0.140 g, 1.44 mmol) was added dropwise to [2-(1*H*-imidazol-4-yl)ethyl]-(5-methylthiazol-2-yl)amine (**8**) (0.30 g, 1.44 mmol) in dry DMF (10 mL). After stirring for 30 min at rt, the solvent was removed in vacuo, and the crude compound was separated by flash chromatography using THF/*n*-hexane (2:8) to afford (5-methylthiazol-2-yl)-{2-[1-(5-methylthiazol-2-yl)-1*H*-imidazol-4-yl]ethyl}amine (**9**) as a white solid (0.37 g, 1.21 mmol, 84%). Recrystallization was conducted from diethyl ether, mp 115−116 °C. IR (KBr): $\tilde{\nu}$ = 3195 (NH), 2923, 1572, 1474, 1144 cm^{-1}; ^1H NMR (300 MHz, CD_3OD): δ = 2.23 (d, ^4J = 1.2 Hz, 3 H, Me), 2.47 (d, ^4J = 1.2 Hz, 3 H, Me), 2.88 (t, J = 6.9 Hz, 2 H, CH_2), 3.53 (t, J = 6.9 Hz, 2 H, NCH_2), 6.63 (q, ^4J = 1.2 Hz, 1 H, =CH), 7.28 (q, ^4J = 1.2 Hz, 1 H, =CH), 7.46 (dt, ^4J = 1.4 Hz, ^4J = 0.9 Hz, 1 H, =CH), 8.22 (d, ^4J = 1.4 Hz, 1 H, =CH); ^1H NMR (300 MHz, $CDCl_3$): δ = 2.25 (d, ^4J = 1.5 Hz, 3 H, Me), 2.45 (d, ^4J = 1.2 Hz, 3 H, Me), 2.91 (t, J = 6.6 Hz, 2 H, CH_2), 3.57 (t, J = 6.6 Hz, 2 H, NCH_2), 5.71 (br, 1 H, NH), 6.70 (q, ^4J = 1.5 Hz, 1 H, =CH), 7.18 (q, ^4J = 1.2 Hz, 1 H, =CH), 7.22 (dt, ^4J = 1.5 Hz, ^4J = 0.9 Hz, 1 H, =CH), 8.02 (d, ^4J = 1.5 Hz, 1 H, =CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.91 (q, Me), 11.93 (q, Me), 27.55 (t, C-2), 44.84 (t, C-1), 114.52 (d), 120.79 (s), 130.57 (s), 134.84 (d), 135.34 (d), 137.51 (d), 141.30 (s), 155.26 (s), 168.67 (s). Anal. Calcd for $C_{13}H_{15}N_5S_2$ (305.43): C 51.12, H 4.95, N 22.93, S 21.00. Found: C 50.52, H 5.00, N 23.04, S 20.70.

Synthesis of *Z*-*N*-(5,5'-Dimethyl-2,3'-bi-thiazol-2'-ylidene)-{2-[1-(5-methylthiazol-2-yl)-1*H*-imidazol-4-yl]ethyl}amine (10):

Method **A**

1-Isothiocyanatopropa-1,2-diene (**4a**) 10% in dry THF (0.16 g, 1.64 mmol) was added dropwise to (5-methylthiazol-2-yl)-{2-[1-(5-methylthiazol-2-yl)-1*H*-imidazol-4-yl]ethyl}amine (**9**) (0.50 g, 1.64 mmol) in dry THF (10 mL). After stirring for 2 h at rt, the solvent was removed in vacuo, and the crude compound was separated by flash chromatography using acetone/*n*-hexane (1:1) to yield *Z*-*N*-(5,5'-dimethyl-2,3'-bi-thiazol-2'-ylidene)-{2-[1-(5-methylthiazol-2-yl)-1*H*-imidazol-4-yl]ethyl}amine (**10**) as a white solid (0.53 g, 1.31 mmol, 80%). Recrystallization was carried out from acetone and *n*-hexane.

Method **B**

1-Isothiocyanatopropa-1,2-diene (**4a**) 10% in dry DMF (1.05 g, 10.8 mmol) was added dropwise to 2-(1*H*-imidazol-4-yl)ethylamine (**1**) (0.30 g, 2.70 mmol) in dry DMF (5 mL). After stirring for 3 h at rt, the solvent was removed in vacuo and the crude compound was separated by flash chromatography utilizing acetone and *n*-hexane (1:1) to furnish *Z*-*N*-(5,5'-dimethyl-2,3'-bi-thiazol-2'-ylidene)-{2-[1-(5-methylthiazol-2-yl)-1*H*-imidazol-4-yl]ethyl}amine (**10**) as a white solid (0.42 g, 2.02 mmol, 51%). Recrystallization was done from acetone and *n*-hexane, mp = 137–142 °C. IR ($CDCl_3$): $\tilde{\nu}$ = 2922, 1650, 1623, 1482, 1145 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ= 2.16 (d, ^4J = 1.2 Hz, 3 H, Me), 2.34 (d, ^4J = 1.2 Hz, 3 H, Me), 2.44 (d, ^4J = 1.2 Hz, 3 H, Me), 3.05 (t, J = 7.1 Hz, 2 H, CH_2), 3.54 (t, J = 7.2 Hz, 2 H, NCH_2), 7.06 (q, ^4J = 1.5 Hz, 1 H, =CH), 7.17 (d, ^4J = 1.2 Hz, 1 H, imidazole-H), 7.34 (q, ^4J = 1.5 Hz, 1 H, =CH), 7.40 (q, ^4J = 1.5 Hz, 1 H, =CH), 8.05 (d, ^4J = 1.2 Hz, 1 H, imidazole-H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ= 11.46 (q, Me), 11.97 (q, Me), 13.76 (q, Me), 29.79 (t, C-2), 53.99 (t, C-1), 113.62 (s), 114.66 (d), 119.17 (d), 127.39 (s), 130.19 (s), 134.10 (d), 134.38 (d), 137.50 (d), 142.71 (s), 152.99 (s), 155.19 (s), 155.67 (s). Anal. Calcd for $C_{17}H_{18}N_6S_3$ (402.57): C 50.72, H 4.51, N 20.88, S 23.90. Found: C 50.82, H 4.62, N 20.22, S 23.43.

Synthesis of 7-(5-Methylthiazol-2-yl)-7*H*-purin-6-ylamine (11):

1-Isothiocyanatopropa-1,2-diene (**4a**) 10% in dry DMF (2.51 g, 25.9 mmol) was added dropwise to 9*H*-purin-6-ylamine (adenine) (**2**) (0.50 g, 3.70 mmol) in dry DMF (10 mL). After stirring for 4 days at rt, the solvent was removed in vacuo, and the crude compound was extracted using hot MeOH to give 7-(5-methylthiazol-2-yl)-7*H*-purin-6-ylamine (**11**) as a beige solid (0.36 g, 1.55 mmol, 42%). Recrystallization was done from MeOH and EtOAc, mp 260–265 °C. IR (KBr): $\tilde{\nu}$ = 3254 (NH_2), 1650 (C=C), 1485 (C=N), 1145 (S–C) cm^{-1}; ^1H NMR (300 MHz, [D_6]DMSO): δ= 2.45 (d, ^4J = 1.2 Hz, 3H, Me), 7.47 (q, ^4J = 1.2 Hz, 1H, =CH), 7.95 (br s, NH_2), 8.26 (s, 1H), 8.89 (s, 1H); ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 11.51 (q, Me), 109.47 (s), 131.67 (s), 136.72 (d), 144.92 (d), 151.92 (s), 153.93 (d), 156.02 (s), 160.05 (s). Anal. Calcd for $C_9H_8N_6S$ (232.27): C 46.55, H 3.45, N 36.21, S 13.79. Found: C 46.38, H 3.60, N 35.76, S 13.70.

Table 1. Crystal data and structure refinement details of compounds **10** and **11**[a]

	10	**11**
Empirical formula	$C_{17}H_{18}N_6S_3$	$C_{10}H_{12}N_6OS$
Formula weight	402.55	264.32
Temperature [K]	298(2)	298(2)
Wavelength [Å]	0.71073	0.71073
Crystal system	triclinic	monoclinic
Space group	$P\bar{1}$	$P2_1/n$
Unit cell dimensions	a = 6.0349(15) Å	a = 7.332(8) Å
	b = 8.321(2) Å	b = 16.103(17) Å
	c = 19.245(5) Å	c = 10.241(10) Å
	α = 99.201(5)°	
	β = 91.218(5)°	β = 101.08(3)°
	γ = 97.225(4)°	
Volume [Å^3]	945.6(4)	1187(2)
Z	2	4
Calculated density [g/cm^3]	1.414	1.480
Absorption coefficient [mm^{-1}]	0.406	0.271
F(000)	420	552
Crystal size	0.4 × 0.05 × 0.05 mm	0.6 × 0.5 × 0.3 mm
θ range for data collection	2.15 to 26.45°	2.39 to 26.72°
Index ranges	$-7 \le h \le 7$	$-9 \le h \le 9$
	$-10 \le k \le 10$	$0 \le k \le 20$
	$-24 \le l \le 24$	$0 \le l \le 12$
Reflections collected	9851	13915
Independent reflections	8905 [R_{int} = 0.0601]	2597 [R_{int} = 0.0743]
Data / restraints / parameters	8905 / 94 / 243	2494 / 0 / 200
Goodness-of-fit on F^2	1.009	1.038
Final $R^{b,c}$ indices [$I^2 > 2\sigma(I)$]	R_1 = 0.0873, wR_2 = 0.2031	R_1 = 0.0638, wR_2 = 0.1499
$R^{b,c}$ indices (all data)	R_1 = 0.1150, wR_2 = 0.2208	R_1 = 0.1101, wR_2 = 0.1728
Largest diff. peak and hole	0.670 and –0.602 e·Å^{-3}	0.482 and –0.333 e·Å^{-3}

[a]Standard uncertainties of the last significant digits are shown in parentheses.

[b] $R_1 = \frac{\sum \| F_o | - | F_c \|}{\sum | F_o |}$. [c] $wR_2 = \sqrt{\frac{\sum w(F_o^2 - F_c^2)^2}{\sum w(F_o^2)^2}}$ with $w = \frac{1}{\sigma^2(F_o^2) + (g_1 P)^2 + g_2 P}$; $P = \frac{(\max(F_o^2, 0) + 2F_c^2)}{3}$.

Table 2. Bond lengths (Å) and angles (°) of hydrogen bonds of **11**[a]

Type	Donor–H---Acceptor	D–H	H---A	D---A	D–H---A
Intra	N10–H3---N11	0.83(4)	2.05(4)	2.790(6)	149(3)
Inter	N10–H4---N1	0.83(4)	2.21(4)	3.041(6)	173(3)
Inter	O1–H9---N3	0.97(6)	1.86(6)	2.808(5)	163(6)

[a]Standard uncertainties of the last significant digits are shown in parentheses.

X-Ray Structure Analysis: Data were collected with a Bruker Smart CCD diffractometer using Mo-Kα radiation (λ = 0.71073 Å). The structures were solved by direct methods using SHELXS-97.[20] The structure was refined by full-matrix least-squares procedures on F^2, using SHELXL-97.[21] All non-hydrogen atoms were refined anisotropically. For compound **10**, the hydrogen atom positions have been added using the idealized positions and refined isotropically. Compound **10** crystallized as a partial merohedral twin of third order. Matrices of both domains have been determined by picking the reflections in the program RLATT and refinement in Smart. Twin refinement has been done with a hklf5 file generated by the program Gemini. Six scaling factors have been given for the ranges of 0 to 0.016 to 0.035 to 0.06. For compound **11**, all hydrogen atom positions less at the methyl group in the methanol solvent molecule have been taken from the difference Fourier map and refined freely. The hydrogen atom positions at C13 have been refined with a riding model. The molecule shows in the crystal a dimeric structure connected via hydrogen bridge bonding (Table 2). Crystal data and structure refinement details of the compounds **10** and **11** are given in Table 1. CCDC-679542 (for **10**) and -679543 (for **11**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.

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REFERENCES

†Part 16 of the series 'Rearrangement Reactions'. For Part 15, see B. Jawabrah Al-Hourani, K. Banert, N. Gomaa, K. Vrobel, *Tetrahedron*, 2008, **64**, 5.

1. J. Sirois, G. Ménard, A. S. Moses, and E. Y. Bissonnette, *J. Immunol.*, 2000, **164**, 2964; D. T. Davies, Aromatic Heterocyclic Chemistry, Oxford University Press, New York, 1992, p. 20; R. Jain and L. A. Cohen, *Tetrahedron*, 1996, **52**, 5363; P. W. Baures, K. Kaliyan and J. Desper, *Molecules*, 2002, **7**, 813.

2. C. E. S. Alvaro and N. S. Nudelman, *J. Phys. Org. Chem.*, 2005, **18**, 880.
3. D. Voet, J. G. Voet, and C. W. Pratt, Lehrbuch der Biochemie (ed. by A. G. Beck-Sickinger and U. Hahn), Wiley-VCH, Weinheim, 2002, p. 45; T. W. G. Solomons and C. B. Fryhle, Organic Chemistry, 7th ed., Wiley, New York, 2000, p. 644.
4. M. Dreyfus, G. Dodin, O. Bensaude, and J. E. Dubois, *J. Am. Chem. Soc.*, 1975, **97**, 2369; M.-T. Chenon, R. J. Pugmire, D. M. Grant, R. P. Panzica, and L. B. Townsend, *J. Am. Chem. Soc.*, 1975, **97**, 4636.
5. N. J. Leonard and T. R. Henderson, *J. Am. Chem. Soc.*, 1975, **97**, 4990.
6. N. Bodor, M. J. S. Dewar, and A. J. Harget, *J. Am. Chem. Soc.*, 1970, **92**, 2929; F. Jordan and H. D. Sostman, *J. Am. Chem. Soc.*, 1972, **94**, 7898.
7. M. Rasmussen and J. M. Hope, *Aust. J. Chem*., 1982, **35**, 525.
8. A. C. Bajji and D. R. Davis, *J. Org. Chem.*, 2002, **67**, 5352; J. Wang and A. Gossauer, *Helv. Chim. Acta*, 1994, **77**, 533; M. D. García, O. Caamaño, F. Fernández, C. López, and E. De Clercq, *Synthesis*, 2005, 925.
9. E. P. Lira and C. W. Huffman, *J. Org. Chem.*, 1966, **31**, 2188.
10. M. Rasmussen and N. J. Leonard, *J. Am. Chem. Soc.*, 1967, **89**, 5439; N. J. Leonard and J. A. Deyrup, *J. Am. Chem. Soc.*, 1962, **84**, 2148.
11. C. C. Price, G. M. Gaucher, P. Koneru, R. Shibakawa, J. R. Sowa, and M. Yamaguchi, *Biochim. Biophys. Acta*, 1968, **166**, 327.
12. K. Banert, H. Hückstädt, and K. Vrobel, *Angew. Chem.*, 1992, **104**, 72; K. Banert, H. Hückstädt, and K. Vrobel, *Angew. Chem., Int. Ed. Engl.*, 1992, **31**, 90; K. Banert, *Liebigs Ann./Recueil*, 1997, 2005.
13. K. Banert, S. Groth, H. Hückstädt, J. Lehmann, J. Schlott, and K. Vrobel, *Synthesis*, 2002, 1423; K. Banert, B. Jawabrah Al-Hourani, S. Groth, K. Vrobel, *Synthesis* 2005, 2920.
14. For reviews on the synthesis of thiazoles, see: D. Kikelj and U. Urleb, in: Science of Synthesis, Vol. 11 (ed. by E. Schaumann), Thieme, Stuttgart, 2002, pp. 627-833; J. Liebscher, in: Houben–Weyl, 4th ed., Vol. E 8b/II (ed. by E. Schaumann), Thieme, Stuttgart, 1994, pp. 1-398; A. Dondoni and P. Merino, in: Comprehensive Heterocyclic Chemistry II, Vol. 3 (ed. by A. R. Katritzky, C. W. Rees, and E. F. V. Scriven), Pergamon, Oxford, 1994, pp. 373-474; S. Sharma, *Sulfur Rep.*, 1989, **8**, 327.
15. For the multi-step synthesis of products similar to **8** via classical Hantzsch procedure, see: P. V. Plazzi, F. Bordi, M. Mor, C. Silva, G. Morini, A. Caretta, E. Barocelli, and T. Vitali, *Eur. J. Med. Chem.*, 1995, **30**, 881.
16. For the reaction of **1** with isothiocyanates, see: C. R. Ganellin, S. K. Hosseini, Y. S. Khalaf, W. Tertiuk, J.-M. Arrang, M. Garbarg, X. Ligneau, and J.-C. Schwartz, *J. Med. Chem.*, 1995, **38**, 3342; J. Isac-Garcia, F. Hernández-Mateo, F. G. Calvo-Flores, and F. Santoyo-González, *J. Org. Chem.*, 2004,

69, 202.

17. Even after a reaction time of 4 days room temperature, we got only product **11**. Higher temperatures are not compatible with **4a** because this starting material tends to polymerization.[13]
18. J. Emsley, D. J. Jones, and J. Lucas, *Rev. Inorg. Chem.*, 1981, **3**, 105.
19. W. C. Still, M. Kahn, and A. Mitra, *J. Org. Chem.*, 1978, **43**, 2923.
20. G. M. Sheldrick, *Acta Crystallogr. Sect. A*, 1990, **46**, 467.
21. G. M. Sheldrick, SHELXL-97, Program for Crystal Structure Refinement, University of Göttingen, 1997.