EurJOC European Journal of Organic Chemistry

FULL PAPER

DOI: 10.1002/ejoc.201301851

Synthesis of Unexpected Bifunctionalized Thiazoles by Nucleophilic Attack on Allenyl Isothiocyanate

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Dedicated to Professor Helmut Quast on the occasion of his 80th birthday

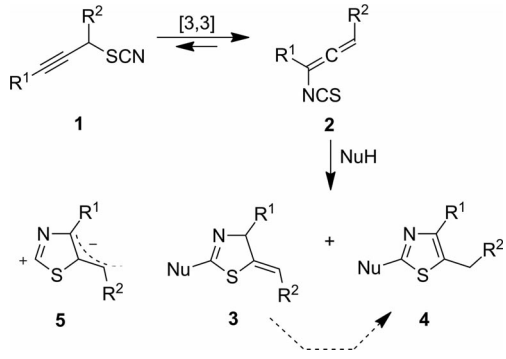
Keywords: Nitrogen heterocycles / Reaction mechanisms / Reactive intermediates / Allenes / Isothiocyanates

Treatment of allenyl isothiocyanate with a variety of nucleophiles leads to 5-methylthiazoles with a functional group at the 2-position. The same pattern of reactivity is also seen with *N*-aminophthalimide. In the presence of azide salt, hydrazoic acid, or *N*,*N*-disubstituted hydroxylamines, however, allenyl isothiocyanate is converted into bifunctionalized thiazoles. We explain the formation of these products by nucleophilic addition at the isothiocyanato moiety followed by ring closure and an N–N or N–O cleavage reaction to generate short-lived 2-imino-5-methylidenethiazole or 5-methylidenethiazol-2-one. Such intermediates are trapped by addition reactions to give the final heterocyclic compounds. In the case of *N*,*N*-disubstituted hydroxylamines, the primary addition products with allenyl isothiocyanate can be detected as unstable intermediates by IR and NMR spectroscopy.

Introduction

Thiazoles are well represented in a variety of biomolecules, and they have diverse biological activities.[1] Most commercially significant compounds of this type are fungicides, drugs, or dyes. Consequently, diverse methods exist for the synthesis of thiazoles.[2] Nevertheless, there is strong demand to prepare such heterocycles by new methods and so obtain, e.g., products with unknown substitution patterns.

Recently, we reported the first synthesis of allenyl isothiocyanates **2** by [3,3]-sigmatropic rearrangement of propargyl thiocyanates **1**, which can be carried out in excellent yields and on a large scale by using flash vacuum pyrolysis (Scheme 1).[3] Highly reactive cumulenes **2** were treated with carbon-, oxygen-, nitrogen-, phosphorus-, sulfur-, or hydride-containing nucleophiles NuH to give thiazole derivatives **3** and **4**. The subsequent rearrangement **3**→**4** gave **4** as a single product.[3e] The unusual reactivity of **2** was seen in its reactions with weak nucleophiles such as diphenylamine[3a,3d] or neutral water in tetrahydrofuran,[3a,3e] which led to thiazole products of type **4** even at room temperature. Compounds **2** proved to be highly selective electrophilic reagents, as shown by exposure to ambident nucleophiles, for example, histamine or adenine.[4] Thus, the chemistry of **2** shows that allenyl isothiocyanates act predominantly as valuable synthetic equivalents of synthons **5**.[5]



Scheme 1. Generation of allenyl isothiocyanates **2** and their transformation into thiazole derivatives **3** and **4**.

In this paper, we describe the surprising reactions of allenyl isothiocyanate (**2a**) with lithium azide, hydrazoic acid, or hydroxylamines with different substitution patterns. In these cases, unexpected bifunctionalized thiazoles, which do not fit into the simple structures **3** and **4**, were obtained as major products.

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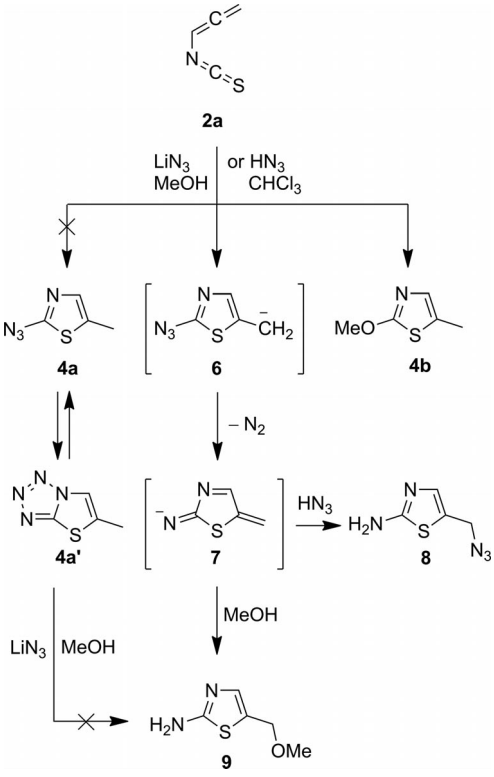
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201301851.

Results and Discussion

When we treated allenyl isothiocyanate (**2a**) with lithium azide in methanol at room temperature, we did not detect any trace of the expected product (i.e., **4a**), which is known[6] to equilibrate with bicyclic tetrazole **4a′** (Scheme 2). Instead, we observed liberation of dinitrogen and, after workup, the formation of bifunctionalized thiazole **9** in 76% yield as well as known[3a,3d,7] methoxythiazole **4b** in 24% yield. Compound **4a/4a′**, which is easily available by nitrosation of (5-methylthiazol-2-yl)hydrazine,[6] was also treated with lithium azide in methanol. This control experiment confirmed that compounds **4b** and **9** were not formed from **4a/4a′** under these conditions.



Scheme 2. Reaction of allenyl isothiocyanate (**2a**) with lithium azide or hydrazoic acid.

Alkyl, aryl, and vinyl isothiocyanates are generally converted into 5-amino-substituted 1,2,3,4-thiatriazoles in the presence of hydrazoic acid by addition at the C=N bond followed by ring closure,[8] whereas treatment with sodium azide in protic solvents leads to the corresponding 1-substituted 5-mercaptotetrazoles.[9] When we treated **2a** with an excess of hydrazoic acid in chloroform at room temperature, we obtained a single product **8** in 60% yield. Structural assignment was based on IR and NMR spectroscopic data and elemental analysis, and was further confirmed by single-crystal X-ray diffraction analysis (Figure 1).[10,11]

A mechanism that explains the formation of the thiazoles **9** and **8** most probably includes initial attack of lithium azide or hydrazoic acid at the carbon atom of the N=C=S unit, and subsequent cyclization to generate anion **6** or the corresponding N_α-protonated species. Thereafter, cleavage

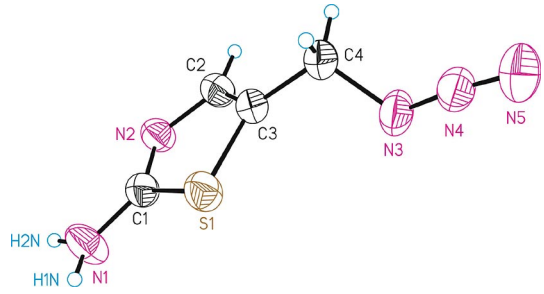
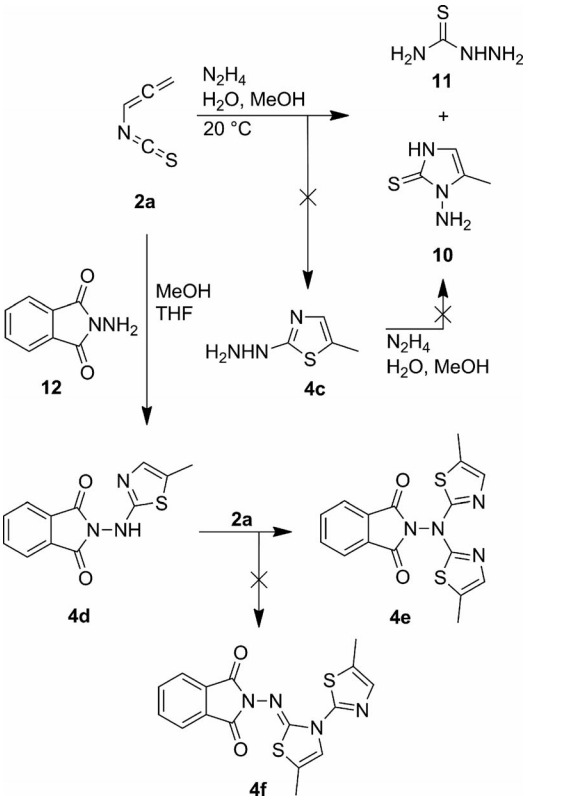


Figure 1. ORTEP diagram (50% ellipsoid probability) of the molecular structure of thiazole **8**.

of the weak N_α–N_β bond with liberation of dinitrogen leads to **7** or the N_α-protonated intermediate. Finally, 1,6-addition of hydrazoic acid or methanol gives rise to aromatic products **8** or **9**, respectively. When **2a** was treated with hexadecyltributylphosphonium azide[12] in aprotic $CDCl_3$ at 0 °C, we observed a rapid reaction with liberation of dinitrogen. However, we were not able to isolate any characterizable product. Thus, we suppose that **7** is a short-lived intermediate that must be trapped under protic conditions. We assume that protonation of intermediate **6** at the CH_2 position to form stable heterocycles **4a/4a′** cannot compete with the rapid cleavage to give dinitrogen. Thus, the weak N_α–N_β bond of azide **6** is responsible for the result that products quite different from those shown in Scheme 1 are generated. Consequently, it should be possible to use other nucleophiles, such as hydrazines with weak N–N bonds or hydroxylamines with cleavable N–O bonds, to obtain bifunctionalized thiazoles analogous to **8** and **9**.

When we treated cumulene **2a** with hydrazine hydrate in methanol, we did not get the expected thiazole derivative (i.e., **4c**) or any product that indicated that cleavage of the hydrazine N–N bond had occurred (Scheme 3). A mixture of thiosemicarbazide (**11**; 77% yield) and the surprising imidazole-2-thione **10** (21%) was obtained instead. When pure hydrazine was used instead of hydrazine hydrate, the yields of the products changed only slightly. The structure of heterocycle **10** was confirmed not only by elemental analysis, IR, MS, ^{1}H NMR, and ^{13}C NMR spectroscopic data, but also by ^{15}N NMR spectroscopic measurements. In a control experiment, we showed that known[13] compound **4c** is stable in the presence of hydrazine hydrate, and that it does not rearrange to the isomeric product **10** under such reaction conditions.

We assumed that the N–N bond in *N*-aminophthalimide (**12**) may be weaker than that in hydrazine. Thus, products resulting from cleavage of this bond should be accessible by treatment of isothiocyanate **2a** with nucleophile **12**. However, treatment of **12** with a 1.5-fold excess of **2a** in THF and methanol led to heterocycles **4d** (12% yield) and **4e** (21%) after 24 h at room temperature. Obviously, the conversion of **2a** was slow, because increasing the reaction time to 48 h resulted in increased yields of **4d** (29%) and **4e** (45%). When a 2.3-fold excess of **2a** was used together with an extended reaction time of 48 h, the ratio of products **4d** (22% yield) and **4e** (57%) changed moderately. The struc-



Scheme 3. Reaction of allenyl isothiocyanate (**2a**) with hydrazine or *N*-aminophthalimide (**12**).

ture of compound **4e** was confirmed from its spectroscopic data as well as by single-crystal X-ray diffraction (Figure 2).[11,14] The formation of this product via intermediate **4d** was surprising; we expected the less symmetrical thiazole derivative **4f** to be formed, but it was not detected. In the case of other monosubstituted 2-aminothiazoles or the parent compound itself, it is well known that the reaction with **2a** starts with nucleophilic attack of the ring atom N-3, and not the exocyclic amine functionality.[3e,4]

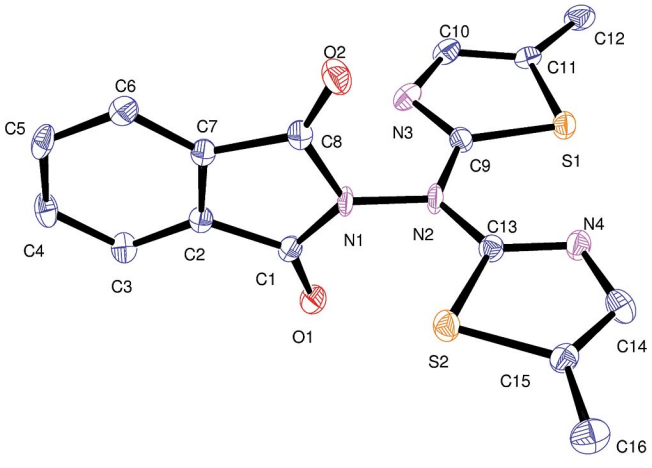
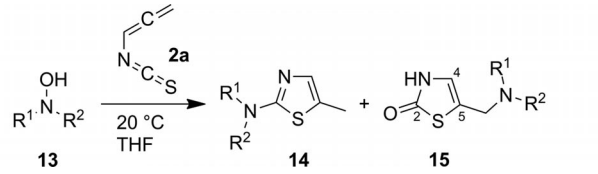


Figure 2. ORTEP diagram (55% ellipsoid probability) of thiazole **4e**.

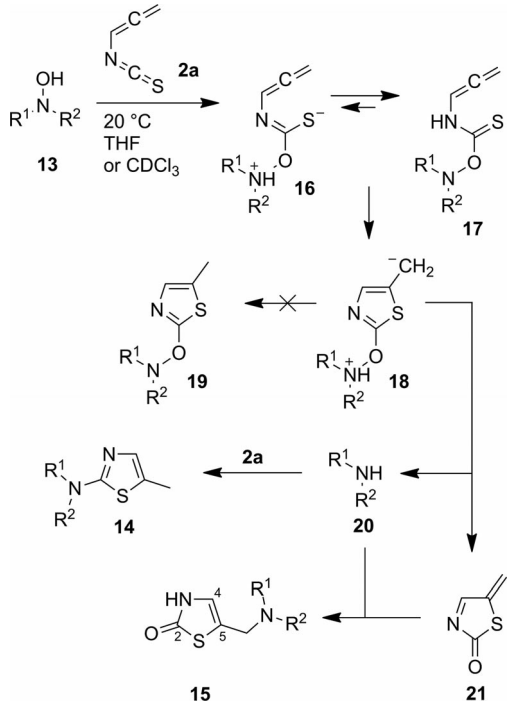
Finally, we treated allenyl isothiocyanate (**2a**) in THF with hydroxylamine derivatives **13** (Table 1). When an excess of **2a** was used, we obtained mixtures of 2-aminothiazoles **14** and bifunctionalized thiazoles **15**. By using excess **13a** or **13b**, we exclusively obtained products **15a** or **15b**, respectively. *O*-(Thiazol-2-yl)hydroxylamines **19** (see Scheme 4), which correspond to product type **4**, were not detected in any case. For comparison, we prepared **14c** (43% yield), **14d** (82%), and even the sterically hindered tertiary amine *N*-(*tert*-butyl)-*N*-isopropyl-5-methylthiazol-2-amine (**14e**; 80% yield) from **2a** and the corresponding secondary amines (i.e., **20c**–**20e**). The synthesis of 2-aminothiazoles **14a**,**b** by alternative methods has been described

Table 1. Reaction of **2a** with **13a**–**13f** in THF.



13	Hydroxylamine		Ratio	Yields [%][a]	
	R^1	R^2	2a/13	14	15
a	Me	Me	1.1:1	29	58
a	Me	Me	1:2	0	55
b	Et	Et	1.5:1	29	55
b	Et	Et	1:2	0	79
c		$-(CH_2)_5-$	2:1	30	40
d	Bn	Bn	1.5:1	33	35
e	*t*Bu	*i*Pr	1.5:1	33	0
f	*t*Bu	*t*Bu	2:1	0[b]	0[b]

[a] Isolated yields based on the substoichiometric starting compound (**2a** or **13**) after separating **14** and **15** by chromatography. [b] No reaction.



Scheme 4. Mechanism to explain the reaction of **2a** with **13** and the formation of **14** and **15**.

in the literature.[15] The structures of products **15a**–**15d** were assigned on the basis of elemental analyses, HRMS data, and especially their IR and NMR spectra. When the IR and NMR spectra of these products were compared with those of the model compound 5-methylthiazol-2(3*H*)-one,[3e,16] good agreement of the corresponding IR absorptions originating from C=O (1645–1660 cm^{-1}) and N–H units (3125–3171 cm^{-1}) as well as similar δ values for the ^{13}C NMR signals of C-2 (δ = 175.9–176.3 ppm), C-4 (δ = 116.3–118.9 ppm), and C-5 (δ = 116.4–120.6 ppm) were seen. The ^{15}N NMR spectrum of **15b** revealed two signals with the expected[16] chemical shifts [δ = –315.8 (NEt_2) and –214.6 (NH–C=O) ppm]. The δ value of the upfield signal in particular is quite different from those of hydroxylamines, for example, **13b**.[17] However, the value of $^1J(^{15}N,^1H)$ could not be measured, probably owing to rapid exchange processes. We assume that the NH tautomer (thiazol-2(3*H*)-one) is the favored structure of **15** in solution. X-ray diffraction analysis proved the predominance of this tautomer also in the single crystal of **15c** (Figure 3).[11,18]

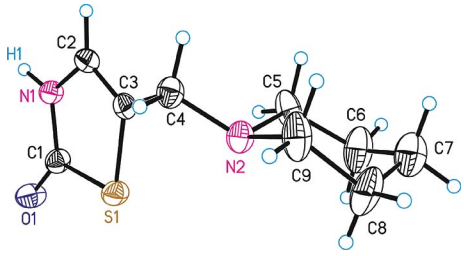


Figure 3. ORTEP diagram (25% ellipsoid probability) of the molecular structure of **15c**. Only one atomic position of disordered atoms is displayed.

We also treated isothiocyanate **2a** with nucleophiles **13** in $CDCl_3$ to investigate the mechanism of formation of products **14** and **15**. When **2a** was treated with an excess of **13**, the conversion of the starting materials within about 15 min at room temperature and the generation of intermediate **17** could be monitored by IR, ^1H NMR, and ^{13}C NMR spectroscopy (Scheme 4 and Table 2). The new functionalized allenes **17** showed an IR absorption at $\tilde{\nu}$ = 1957–1964 cm^{-1}, and the detection of a vicinal CH–NH coupling in the ^1H NMR spectra, for example, ^3J = 9.8 Hz in the case of **17d**, demonstrated that the depicted NH–C=S tautomer is predominant. When compounds **17** were stored in solution at ambient temperature for approximately 24 h, or upon attempted chromatography on silica gel, they isomerized to give compounds **15**. In this conversion, and also in the reaction of **2a** with an excess of **13** (see above), no signals of **14** were observed. Allenes **17** are the first open-chain intermediates to be detected after treatment of cumulenes **2** with nucleophiles to generate thiazole derivatives.

When we treated **13** with excess **2a**, mixtures of **14** and **15** were formed. The product distribution formed in the reaction of **13b** in particular was strongly dependent on the molar ratio of isothiocyanate to hydroxylamine. Thus, a twofold excess of **2a** led exclusively to 2-aminothiazole **14b** (58% yield).

To explain the formation of heterocyclic products **14** and **15**, the mechanism shown in Scheme 4 is suggested. After nucleophilic addition of **13** to the isothiocyanate moiety of **2a**, intermediate **17** most probably cyclizes to give dipolar species **18**. Obviously, proton transfer (i.e., **18**→**19**) cannot compete with cleavage of **18** to give secondary amine **20** and highly reactive compound **21**. The latter undergoes a 1,4-addition with **20** to give final product **15**. If an excess of **13** is used, **2a** is rapidly and completely consumed, and therefore production of **14** from **2a** and **20** is not possible. In the presence of excess **2a**, however, **20** liberated from **18** also attacks **2a** to give **14**. A great excess of **2a** (at least 2 equiv.) is able to completely transform in-situ-generated trapping reagent **20** into **14**. In this case, the interception reaction (i.e., **20** + **21**→**15**) is prevented.

We cannot completely exclude a direct rearrangement of **18** to give **15** without the formation of **21**. But the corresponding migration of the amino functionality seems to be electronically unfavorable, and a synchronous process is impossible for geometrical reasons.

When an excess of **2a** was treated with sterically hindered hydroxylamines **13e**[19] or **13f**,[19] only the former nucleophile was able to attack the isothiocyanate, and no reaction occurred with **13f**. Owing to its severe steric hindrance, the liberated amine (i.e., **20e**) obviously cannot trap short-lived intermediate **21**, but the reactivity of the amine is sufficient to produce **14e** in the presence of **2a** (Table 1).

Table 2. Reaction of **2a** with **13a**–**13d**, and **13f** in $CDCl_3$.

13	Hydroxylamine		Ratio	Yields [%][a]		
	R^1	R^2	**2a/13**	**17**[b]	**14**[c]	**15**[c]
a	Me	Me	1:2	100	0	84
a	Me	Me	2:1	100	62	21
b	Et	Et	1:2	86	0	60
b	Et	Et	1.5:2	–[d]	35	41
b	Et	Et	2:1	92	58	0
c		$–(CH_2)_5–$	1:2	83	0	51
d	Bn	Bn	1:2	80	0	61
f	*t*Bu	*t*Bu	1:2	0[e]	0[e]	0[e]

[a] Yields based on the substoichiometric starting compound (**2a** or **13**) and ^1H NMR standard after monitoring of the reaction. [b] After about 15 min at room temperature. [c] After approximately 24 h at room temperature. [d] Not analyzed. [e] No reaction.

Conclusions

In summary, we have prepared several unexpected bifunctionalized thiazole derivatives by treating allenyl isothiocyanate (**2a**) with nucleophiles such as lithium azide or hydroxylamines. The formation of these products can easily be explained by mechanisms involving nucleophilic addition to **2a** and ring closure to generate thiazole intermediates. These intermediates undergo cleavage reactions to give highly unsaturated species **7** and **21**. These then add methanol, hydrazoic acid, or secondary amines to give thiazoles with new substitution patterns. We assume that these new synthetic methods can also be used with substituted allenyl isothiocyanates **2**,[3] and possibly also with other nucleo-

philes with weak bonds, such as hydroperoxides or peroxycarboxylates.

Experimental Section

Caution! Care must be taken in handling azides, which are explosive. Neat azides in particular can lead to large explosions on friction, impact, or heating. Neat allene **2a** can spontaneously polymerize in a highly exothermic reaction. Thus, larger amounts of this substance should be handled in solution.

General Methods: Melting points were determined with a Pentakon Dresden Boetius apparatus. FTIR spectra were recorded with a Bruker IFS 28 FTIR spectrophotometer. Solutions in KBr cuvettes, KBr pellets, or neat films were used for the IR measurements. ^{1}H NMR spectra were recorded with AC-200 (Bruker), Varian Gemini 2000, or Unity Inova 400 spectrometers operating at 200, 300, and 400 MHz, respectively. Using the same spectrometers, ^{13}C NMR spectroscopic data were recorded at 50, 75, and 100 MHz. NMR signals were referenced to tetramethylsilane (TMS; δ = 0 ppm), or to solvent signals and then recalculated relative to TMS. The multiplicities of ^{13}C NMR signals were determined with the aid of DEPT135 experiments. ^{15}N NMR spectra were measured at 30.4 and 40.5 MHz, using $MeNO_2$ as external standard (δ = 0 ppm). MS and HRMS (ESI) spectra were recorded with an Applied Biosystems Mariner 5229 mass spectrometer or a Bruker micrOTOF-QII spectrometer. MS (EI) spectra were conducted with a Hewlett Packard 5988 A spectrometer. GC–MS (EI) was carried out with a GC–MS-QP 5000 quadrupole mass spectrometer (70 eV) from Shimadzu using helium as carrier gas. Elemental analyses were carried out with a Vario EL elemental analyzer from Elementar Analysensysteme GmbH Hanau, or with a Vario Micro Cube from Elementar. TLC was carried out with Macherey–Nagel Polygram SIL G/UV_{254} polyester sheets.

Reaction of 2a with Lithium Azide in Methanol: Freshly prepared allene **2a**[3c] (0.66 g, 6.8 mmol) was slowly added to a stirred solution of lithium azide (1.00 g, 20.4 mmol) in methanol (20 mL) at 0 °C. Liberation of a gas (N_2) immediately occurred. The mixture was stirred at room temperature for 2 d. Then the solvent was removed in vacuo, and the residue was intensively extracted with CH_2Cl_2. The organic layers were dried ($MgSO_4$). The solvent was removed in vacuo to give a mixture of **4b** and **9** (0.96 g; 0.21 g of **4b**, 24%; 0.75 g of **9**, 76%), which was analyzed by ^{1}H NMR spectroscopy. The compound **9** was separated and purified by sublimation at 60 °C/0.001 Torr.

5-(Methoxymethyl)thiazol-2-ylamine (9): Colorless solid, m.p. 96–97 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.32 (s, 3 H, OMe), 4.44 (br. s, 2 H, CH_2), 5.38 (br. s, 2 H, NH_2), 6.94 (br. s, 1 H, =CH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 57.1 (q, OMe), 66.7 (t, CH_2), 127.2 (s, C-5), 137.9 (d, C-4), 169.2 (s, C-2) ppm. MS (70 eV, EI): *m*/*z* (%) = 144 (23) $[M]^+$, 113 (100), 86 (20), 45 (40). $C_5H_8N_2OS$ (144.19): calcd. C 41.65, H 5.59, N 19.43; found C 41.49, H 5.67, N 19.30.

5-(Azidomethyl)thiazol-2-ylamine (8): A dried solution of hydrazoic acid in chloroform was prepared from sodium azide (6.50 g, 100 mmol) in water (20 mL) and chloroform (40 mL), by slow addition of concentrated sulfuric acid (96%; 4.93 g, 2.8 mL, 50.3 mmol) following a standard procedure.[20] Compound **2a** (10% solution in $CHCl_3$; 0.200 g, 2.06 mmol) was added to this solution. The mixture was stirred at room temperature for 3 d in the dark. Then the excess hydrazoic acid and the solvent were removed in vacuo, and the residue was purified by flash chromatography with *n*-hexane/THF, 6:4. The product was recrystallized from CH_2Cl_2/*n*-hexane to give **8** (0.19 g, 60%) as yellow needles, m.p. 87–88 °C. IR (neat): $\tilde{\nu}$ = 3410 (NH_2), 2101 (N_3), 1619, 1517 cm^{-1}. ^{1}H NMR (300 MHz, C_6D_6): δ = 3.49 (br. s, 2 H, CH_2N_3), 3.77 (br. s, 2 H, NH_2), 6.68 (t, ^4J = 0.9 Hz, 1 H, 4-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 47.2 (t, CH_2N_3), 121.0 (s, C-5), 138.6 (d, C-4), 169.3 (s, C-2) ppm. $C_4H_5N_5S$ (155.20): calcd. C 30.96, H 3.25, N 45.13; found C 31.15, H 3.48, N 44.99.

Reaction of 2a with Hydrazine Hydrate: Allene **2a** (2.00 g, 20.6 mmol) was added dropwise to a stirred mixture of hydrazine hydrate (80%; 50.0 mL, 1.03 mol) and methanol (50 mL) at 0 °C. The mixture was stirred at room temperature for 24 h, then the methanol and the excess hydrazine hydrate were removed by distillation at 100 °C/26 mbar. The residue consisted of **10** (0.56 g, 21%) and **11** (1.45 g, 77%). This mixture was treated with CH_2Cl_2 in a Soxhlet apparatus for 3 d to give different fractions of the more soluble **10**. Compound **10** was then purified by recrystallization from $CHCl_3$. The less soluble compound **11** that remained in the Soxhlet thimble was identical with commercially sourced **11**, as shown by ^{1}H and ^{13}C NMR spectroscopic data, m.p., and m.p. of the corresponding mixture (no depression). When pure hydrazine was used instead of hydrazine hydrate, the yields of **10** and **11** changed to 25 and 71%, respectively.

1-Amino-5-methylimidazole-2(3*H*)-thione (10): Colorless solid, m.p. 201 °C (decomp.). IR ($CHCl_3$): $\tilde{\nu}$ = 3660, 3600, 3020 cm^{-1}. ^{1}H NMR (200 MHz, [D$_6$]DMSO): δ = 2.05 (d, ^4J = 1.2 Hz, 3 H, Me), 5.43 (s, 2 H, NH_2), 6.55 (q, ^4J = 1.2 Hz, 1 H, 4-H), 11.58 (br. s, 1 H, NH) ppm. ^{13}C NMR (50 MHz, [D$_6$]DMSO): δ = 9.4 (q, Me), 108.1 (d, C-4), 125.8 (s, C-5), 157.7 (s, C-2). ^{15}N NMR (40.5 MHz, [D$_6$]DMSO): δ = –311.2 (t, ^1J = 68 Hz, NH_2), –222.4 (br. d, $^1J \approx$ 90 Hz, N-3), –195.3 (s, N-1) ppm. MS (70 eV, EI): *m*/*z* (%) = 129 (100) $[M]^+$, 86 (18), 71 (20). $C_4H_7N_3S$ (129.18): calcd. C 37.19, H 5.46, N 32.53, S 24.82; found C 37.24, H 5.74, N 32.36, S 24.77.

Reaction of 2a with *N*-Aminophthalimide (12): Allene **2a** (10% in dry THF; 222 mg, 2.30 mmol) was added to a solution of *N*-aminophthalimide (**12**; 161 mg, 1.00 mmol) in methanol (5 mL). The mixture was stirred for 2 d at room temperature, then a white precipitate of pure bisthiazole **4e** was filtered off. The filtrate was concentrated in vacuo, and the reside was purified by flash chromatography with Et_2O/hexane, 1:1 to 3:1 to give first **4e** (204 mg as total amount, 0.57 mmol, 57%) and then **4d** (56 mg, 0.22 mmol, 22%) as colorless solids, which were recrystallized from $CHCl_3$.

2-(5-Methylthiazol-2-ylamino)isoindoline-1,3-dione (4d): Colorless needles, m.p. 190 °C (decomp.). IR (KBr): $\tilde{\nu}$ = 2920, 1738 (C=O), 1597 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.26 (d, ^4J = 1.2 Hz, 3 H, Me), 6.80 (q, ^4J = 1.2 Hz, 1 H, 4-H), 7.79 (dd, *J* = 5.6, 3.2 Hz, 2 H), 7.91 (dd, *J* = 5.6, 3.2 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.1 (q, Me), 123.9 (d), 124.1 (s, C-5), 130.1 (s), 133.3 (d, C-4), 134.6 (d), 165.4 (s, C-2), 168.0 (s, 2 C=O) ppm. HRMS (ESI$^+$): calcd. for $C_{12}H_{10}N_3O_2S$ $[M + H]^+$ 260.0494; found 260.0471; calcd. for $C_{12}H_9N_3O_2SNa$ $[M + Na]^+$ 282.0313; found 282.0283.

2-[Bis(5-methylthiazol-2-yl)amino]isoindoline-1,3-dione (4e): Yellow crystals, m.p. 265 °C (decomp.). IR (KBr): $\tilde{\nu}$ = 3422 (NH), 3022, 2919, 2857, 1761 (C=O), 1524 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.35 (d, ^4J = 1.2 Hz, 6 H, 2 Me), 7.00 (q, ^4J = 1.2 Hz, 2 H, 2 4-H), 7.87 (dd, *J* = 5.6, 3.2 Hz, 2 H), 8.01 (dd, *J* = 5.6, 3.2 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.7 (q, 2 Me), 124.6 (d), 127.7 (s), 129.8 (s), 135.2 (d), 135.6 (d), 159.6 (s, C-2), 164.5 (s, 2 C=O) ppm. HRMS (ESI$^+$): calcd. for $C_{16}H_{13}N_4O_2S_2$ $[M + H]^+$ 357.0480; found 357.0443; calcd. for $C_{16}H_{12}N_4O_2S_2Na$ [M + Na]

$^{+}$ 379.0299; found 379.0262; calcd. for $C_{16}H_{12}N_4O_2S_2K$ $[M + K]^+$ 395.0039; found 394.9992.

Reaction of Allene 2a with *N*,*N*-Dimethylhydroxylamine (13a): 1-Isothiocyanatopropa-1,2-diene (**2a**; 10% in dry THF; 445 mg, 4.58 mmol) was added dropwise under nitrogen to *N*,*N*-dimethylhydroxylamine (**13a**)[21] (260 mg, 4.26 mmol) in dry THF (10 mL) at –5 °C. After 1 h at –5 °C, the reaction mixture was stirred overnight at room temperature. The solvent was removed under vacuum, and the crude products were separated by flash column chromatography using first diethyl ether/*n*-hexane, 4:6 to give dimethyl-(5-methyl-thiazole-2-yl)-amine (**14a**; 175 mg, 1.23 mmol, 29%), followed by elution with methanol/diethyl ether, 7:93 to give 5-(dimethylaminomethyl)thiazol-2(3*H*)-one (**15a**; 389 mg, 2.46 mmol, 58%). Compound **15a** was recrystallized from diethyl ether and *n*-hexane. Treatment of **2a** with a twofold excess of **13a** was carried out similarly.

Dimethyl-(5-methylthiazol-2-yl)amine (14a): Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.23 (d, ^4J = 1.2 Hz, 3 H, Me-5), 2.98 (s, 6 H, NMe_2), 6.75 (q, ^4J = 1.2 Hz, 1 H, 4-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.9 (q, Me-5), 40.0 (q, NMe_2), 120.9 (s, C-5), 136.3 (d, C-4), 170.4 (s, C-2) ppm. GC–MS: *m*/*z* (%) = 142 (47) $[M]^+$, 113 (89), 100 (30), 71 (54), 44 (100).

5-(Dimethylaminomethyl)thiazol-2(3*H*)-one (15a): Colorless solid, m.p. 105 °C. IR (CCl_4): $\tilde{\nu}$ = 3125 (NH), 2997, 1645 (C=O) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.24 (s, 6 H, NMe_2), 3.29 (d, ^4J = 1.2 Hz, 2 H, NCH_2), 6.46 (t, ^4J = 1.2 Hz, 1 H, 4-H), 10.1 (br. s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 44.7 (q, NMe_2), 57.1 (t, NCH_2), 118.0 (s, C-5), 119.3 (d, C-4), 176.1 (s, C-2) ppm. HRMS (ESI^+): calcd. for $C_6H_{11}N_2OS$ $[M + H]^+$ 159.0592; found 159.0582; calcd. for $C_6H_{10}N_2NaOS$ $[M + Na]^+$ 181.0412; found 181.0410.

Reaction of Allene 2a with *N*,*N*-Diethylhydroxylamine (13b): Following the procedure described for the reaction with hydroxylamine **13a**, *N*,*N*-diethylhydroxylamine (**13b**; 0.20 g, 2.25 mmol) was treated with allene **2a** (0.33 g, 3.37 mmol) to give **14b** (0.11 g, 0.65 mmol, 29%) and **15b** (0.21 g, 1.25 mmol, 55%). Treatment of **2a** with a twofold excess of **13b** was carried out similarly.

Diethyl-(5-methylthiazol-2-yl)amine (14b): Colorless oil. IR (neat): $\tilde{\nu}$ = 2971, 1539, 1120 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.19 (t, ^3J = 7.0 Hz, 6 H, CH_2*Me*), 2.61 (d, ^4J = 1.2 Hz, 3 H, Me-5), 3.41 (q, ^3J = 7.0 Hz, 4 H, C*H*$_2$Me), 6.75 (q, ^4J = 1.2 Hz, 1 H, 4-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.8 (q, Me-5), 12.5 (q, CH_2*Me*), 45.0 (t, CH_2), 119.6 (s, C-5), 136.0 (d, C-4), 168.8 (s, C-2) ppm. GC–MS: *m*/*z* (%) = 170 (27) $[M]^+$, 155 (18), 141 (41), 127 (100), 73 (32).

5-(Diethylaminomethyl)thiazol-2(3*H*)-one (15b): Colorless solid, m.p. 80–82 °C. IR (CCl_4): $\tilde{\nu}$ = 3148 (NH), 2972, 1659 (C=O), 1096 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.02 (t, ^3J = 7.2 Hz, 6 H, CH_2*Me*), 2.55 (q, ^3J = 7.2 Hz, 4 H, C*H*$_2$Me), 3.46 (d, ^4J = 1.2 Hz, 2 H, CH_2 at C-5), 6.44 (t, ^4J = 1.2 Hz, 1 H, 4-H), 9.49 (br. s, 1 H, NH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.7 (q, CH_2*Me*), 46.3 (t, C*H*$_2$Me), 50.7 (t, CH_2 at C-5), 117.1 (d, C-4), 120.6 (s, C-5), 176.1 (s, C-2) ppm, assignments by C–H shift correlation. ^{15}N NMR (30.4 MHz, $CDCl_3$): δ = –315.8 (s, NEt_2), –214.6 (d, N-3) ppm. HRMS (ESI^+): calcd. for $C_8H_{15}N_2OS$ $[M + H]^+$ 187.0900; found 187.0903. $C_8H_{14}N_2OS$ (186.28): calcd. C 51.58, H 7.58, N 15.04, S 17.21; found C 51.61, H 7.35, N 14.94, S 16.90.

Reaction of Allene 2a with *N*-Hydroxypiperidine (13c): Following the procedure described for the reaction with hydroxylamine **13a**, piperidin-1-ol (**13c**; 0.100 g, 0.990 mmol) was treated with allene **2a** (0.190 g, 1.96 mmol) to give **14c** (0.054 g, 0.296 mmol, 30%) and **15c** (0.078 g, 0.390 mmol, 40%).

2-(Piperidin-1-yl)-5-methylthiazole (14c): Colorless oil. IR (CCl_4): $\tilde{\nu}$ = 2942, 1516, 1122 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.61–1.67 (m, 6 H, 3′-H, 4′-H, 5′-H), 2.27 (d, ^4J = 1.2 Hz, 3 H, Me-5), 3.38 (m, 4 H, 2′-H, 6′-H), 6.78 (q, ^4J = 1.2 Hz, 1 H, 4-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.9 (q, Me-5), 24.1 (t, C-4′), 24.9 (t, C-3′, C-5′), 49.4 (t, C-2′, C-6′), 121.0 (s, C-5), 135.9 (d, C-4), 171.0 (s, C-2) ppm. GC–MS: *m*/*z* (%) = 182 (52) $[M]^+$, 153 (56), 126 (64), 99 (40), 72 (52), 41 (100). HRMS (ESI^+) calcd. for $C_9H_{15}N_2S$ $[M + H]^+$ 183.0956; found 183.0997. $C_9H_{14}N_2S$ (182.29): calcd. C 59.30, H 7.74, N 15.37; found C 59.59, H 7.16, N 15.48.

5-(Piperidin-1-ylmethyl)thiazol-2(3*H*)-one (15c): Colorless solid, m.p. 136–138 °C. IR (CCl_4): $\tilde{\nu}$ = 3138 (NH), 2936, 1659 (C=O), 1097 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.41 (m, 2 H, 4′′-H), 1.56 (m, 4 H, 3′′-H and 5′′-H), 2.38 (m, 4 H, 2′′-H and 6′′-H), 3.33 (d, ^4J = 0.9 Hz, 2 H, 1′-H), 6.44 (t, ^4J = 0.9 Hz, 1 H, 4-H), 9.87 (br. s, 1 H, NH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.0 (t, C-4′′), 25.6 (t, C-3′′, C-5′′), 53.8 (t, C-2′′, C-6′′), 56.4 (t, C-1′), 118.1 (d, C-4), 118.9 (s, C-5), 176.3 (s, C-2) ppm. MS (ESI^+): *m*/*z* = 199.08 $[M + H]^+$. $C_9H_{14}N_2OS$ (198.29): calcd. C 54.52, H 7.12, N 14.13, S 16.17; found C 54.45, H 6.83, N 13.91, S 16.81.

Reaction of Allene 2a with *N*,*N*-Dibenzylhydroxylamine (13d): Following the procedure described for the reaction of hydroxylamine **13a**, *N*,*N*-dibenzylhydroxylamine (**13d**; 0.20 g, 0.94 mmol) was treated with allene **2a** (0.14 g, 1.44 mmol) to give **14d** (0.09 g, 0.31 mmol, 33%) and **15d** (0.10 g, 0.32 mmol, 35%).

2-Dibenzylamino-5-methylthiazole (14d): Colorless oil. IR (CCl_4): $\tilde{\nu}$ = 3063, 2920, 1533, 1212 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.31 (d, ^4J = 1.2 Hz, 3 H, Me-5), 4.64 (s, 4 H, 1′-H), 6.86 (q, ^4J = 1.2 Hz, 1 H, 4-H), 7.25–7.37 (m, 10 H, 2 Ph) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.0 (q, Me-5), 53.3 (t, C-1′), 120.9 (s, C-5), 127.4 (d), 127.6 (d), 128.6 (d), 136.1 (d, C-4), 136.8 (s), 170.3 (s, C-2) ppm. GC–MS: *m*/*z* (%) = 294 (2) $[M]^+$, 203 (26), 91 (100), 65 (35). $C_{18}H_{18}N_2S$ (294.42): calcd. C 73.34, H 6.16, N 9.51, S 10.89; found C 73.11, H 5.96, N 9.36, S 11.07.

5-[(Dibenzylamino)methyl]thiazol-2(3*H*)-one (15d): Colorless solid, m.p. 169–170 °C. IR (CCl_4): $\tilde{\nu}$ = 3171 (NH), 1658 (C=O), 1493, 1120, 1097 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.43 (s, 2 H, 1′-H), 3.59 (s, 4 H, 2 C*H*$_2$Ph), 6.45 (s, 1 H, 4-H), 7.24–7.41 (m, 10 H, 2 Ph), 9.74 (br. s, 1 H, NH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 51.0 (t, C-1′), 57.3 (t), 117.5 (d, C-4), 120.4 (s, C-5), 127.1 (d), 128.3 (d), 128.7 (d), 138.7 (s), 175.9 (s, C-2) ppm. HRMS (ESI^+): calcd. for $C_{18}H_{19}N_2OS$ $[M + H]^+$ 311.1218; found 311.1213.

Reaction of Allene 2a with *N*-(*tert*-Butyl)-*N*-isopropylhydroxylamine (13e): Following the procedure described for the reaction with hydroxylamine **13a**, *N*-(*tert*-butyl)-*N*-isopropyl-hydroxylamine (**13e**; 0.200 g, 1.52 mmol) was treated with allene **2a** (0.222 g, 2.29 mmol) to give **14e** (0.106 g, 0.499 mmol, 33%; for characterization data, see below).

2-(Piperidin-1-yl)-5-methylthiazole (14c) and 2-Dibenzylamino-5-methylthiazole (14d): 1-Isothiocyanatopropa-1,2-diene (**2a**; 0.20 g, 2.06 mmol) in THF (2 mL) was added slowly at 0 °C to a solution of piperidine (**20c**; 0.42 g, 4.93 mmol) or dibenzylamine (**20d**; 0.36 g, 4.92 mmol) and toluene-4-sulfonic acid monohydrate (0.47 g, 2.47 mmol) in THF (4 mL) and water (2 mL). The mixture was stirred for 3 d at room temperature, then water (10 mL) was added, and the product was extracted with diethyl ether (3 × 10 mL). The organic layers were combined, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography (diethyl ether/*n*-hexane, 2:8 and 3:8, respec-

tively) to give **14c** (0.16 g, 0.88 mmol, 43%) and **14d** (0.50 g, 1.68 mmol, 82%) as colorless oils.

***N*-(*tert*-Butyl)-*N*-isopropyl-5-methylthiazol-2-amine (14e):** *N*-Isopropyl-*tert*-butylamine (**20e**; 115 mg, 1.00 mmol) was added to a solution of allenyl isothiocyanate (**2a**; 146 mg, 1.50 mmol) in anhydrous THF (5 mL) at 0 °C. The mixture was stirred for 10 h at room temperature, then the solvent was removed under reduced pressure. The crude product was purified by flash chromatography with Et_2O/hexane, 1:20 to 1:15 to give **14e** (169 mg, 0.80 mmol, 80%) as a colorless oil. IR (CCl_4): $\tilde{\nu}$ = 2974, 2926, 2869, 1536 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.13 (d, ^3J = 7.0 Hz, 6 H, $CH(CH_3)_2$), 1.30 [s, 9 H, $C(CH_3)_3$], 2.35 (s, 3 H, Me-5), 3.68 [sept, ^3J = 7.0 Hz, 1 H, $CH(CH_3)_2$], 7.06 (s, 1 H, 4-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.5 (q, Me-5), 23.3 [q, $CH(CH_3)_2$], 28.9 [q, $C(CH_3)$], 47.4 [d, $CH(CH_3)_2$], 57.0 [s, $C(CH_3)_3$], 129.3 (s, C-5), 135.3 (d, C-4), 167.1 (s, C-2) ppm. HRMS (ESI^+): calcd. for $C_{14}H_{19}N_2S$ $[M + H]^+$ 247.1269; found 247.1282; calcd. for $C_{14}H_{18}N_2SNa$ $[M + Na]^+$ 269.1088; found 269.1099.

Detection of Allene Intermediates 17a–17d and Thiazoles 15a–15d in NMR and IR Monitoring Experiments: Hydroxylamines **13a–13d** (2 equiv.) were added to 1-isothiocyanatopropa-1,2-diene (**2a**; 10% in dry $CDCl_3$: 1 equiv.) at –5 °C. After 10, 13, 15, and 17 min, respectively, ^1H NMR and IR spectra showed no remaining allene **2a**. The percentage yields were measured using naphthalene or grease as standard, and found to be 100, 86, 83, and 80% for **17a**, **17b**, **17c**, and **17d**, respectively. After 24, 18, 20, and 21 h, respectively, at room temperature, the reactions were completed to give one major product in each case, i.e., thiazoles **15a**–**15d** with yields of 84, 60, 51, and 61%, respectively (grease was also used as a standard). After 10–17 min as well as after 18–24 h, no signals of **14** could be observed. Experiments with **13a**,**b** and excess amounts of **2a**, which led to detection of **14a**,**b**, **15a**,**b**, and **17a**,**b**, were carried out similarly.

***O*-Dimethylamino *N*-Propa-1,2-dienylthiocarbamate (17a):** IR ($CDCl_3$): $\tilde{\nu}$ = 1962 (w, allene) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.80 (s, 6 H, NMe_2), 5.36 (d, ^4J = 6.4 Hz, 2 H, $=CH_2$), 7.29 (t, ^4J = 6.4 Hz, 1 H, =CH), 9.38 (br. s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 47.9 (q, NMe_2), 86.6 (t, $=CH_2$), 97.0 (d, =CH), 184.5 (s, C=S), 202.8 (s, =C=) ppm.

***O*-Diethylamino *N*-Propa-1,2-dienylthiocarbamate (17b):** IR ($CDCl_3$): $\tilde{\nu}$ = 1964 (w, allene) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.08 (t, ^3J = 7.2 Hz, 6 H, 2 Me), 2.95 (q, ^3J = 7.2 Hz, 4 H, 2 CH_2), 5.33 (d, ^4J = 6.6 Hz, 2 H, $=CH_2$), 7.25 (t, ^4J = 6.6 Hz, 1 H, =CH), 9.42 (br. s, 1 H, NH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.6 (q, 2 Me), 53.3 (t, 2 CH_2), 86.5 (t, $=CH_2$), 96.9 (d, =CH), 186.2 (s, C=S), 202.5 (s, =C=) ppm.

***O*-Piperidin-1-yl *N*-Propa-1,2-dienylthiocarbamate (17c):** IR ($CDCl_3$): $\tilde{\nu}$ = 1960 (w, allene) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.22 (br. qt, J = 13.2, 3.0 Hz, 1 H), 1.62 (qd, J = 11.6, 3.8 Hz, 3 H), 1.83 (dm, J = 13.0 Hz, 2 H), 2.80 (dt, J = 11.0, 3.0 Hz, 2 H), 3.26 (br. dt, J = 9.9, 3.0 Hz, 2 H), 5.33 (d, ^4J = 6.6 Hz, 2 H, $=CH_2$), 7.24 (t, ^4J = 6.6 Hz, 1 H, =CH), 9.46 (br. s, 1 H, NH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.5 (t), 25.1 (t, 2 CH_2), 56.8 (t, 2 CH_2), 86.6 (t, $=CH_2$), 96.9 (d, =CH), 184.5 (s, C=S), 202.6 (s, =C=) ppm.

***O*-Dibenzylamino *N*-Propa-1,2-dienylthiocarbamate (17d):** IR ($CDCl_3$): $\tilde{\nu}$ = 1957 (w, allene) cm^{-1}. ^1H NMR (300 MHz $CDCl_3$): δ = 4.13 (s, 4 H, 2 CH_2), 5.24 (d, ^4J = 6.6 Hz, 2 H, $=CH_2$), 6.84 (dt, ^3J = 9.9, ^4J = 6.6 Hz, 1 H, =CH), 7.32 (m, 10 H, 2 Ph), 8.72 (d, ^3J = 9.3 Hz, 1 H, NH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 62.7 (t, 2 CH_2), 86.1 (t, $=CH_2$), 96.6 (d, =CH), 128.2 (d), 128.6 (d), 129.5 (d), 134.3 (s), 184.5 (s, C=S), 202.3 (s, =C=) ppm.

Supporting Information (see footnote on the first page of this article): Copies of the ^1H and ^{13}C NMR spectra of all new compounds, and detailed crystallographic information.

Acknowledgments

B. J. A.-H. thanks the Deutscher Akademischer Austauschdienst (DAAD) for a PhD fellowship. The authors are indebted to Dr. A. Ihle for assistance with the manuscript, and to Dr. S. Groth for some control experiments. M. K. is grateful to the Fonds der Chemischen Industrie for a PhD fellowship.

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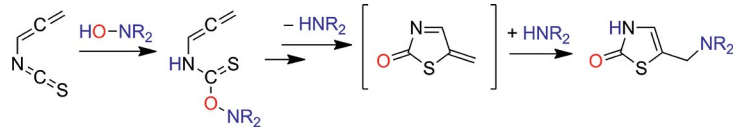
Received: December 12, 2013
Published Online: ■

EurJOC European Journal of Organic Chemistry



Treatment of allenyl isothiocyanate with hydroxylamines led to 5-aminomethylthiazol-2(3*H*)-ones. *O*-Amino *N*-allenylthiocarbamates could be detected as intermediates. Thus, an addition–cyclization–cleavage–addition mechanism via the short-lived 5-methylidenethiazol-2(5*H*)-one is proposed. The reaction of the isothiocyanate with azide salt or hydrazoic acid gave comparable results.

Keywords: Nitrogen heterocycles / Reaction mechanisms / Reactive intermediates / Allenes / Isothiocyanates

