2-CYANAMIDOTHIAZOLES FROM 3-PROPYNYLTHIO-1,2,4-TRIAZOLES [⊥]

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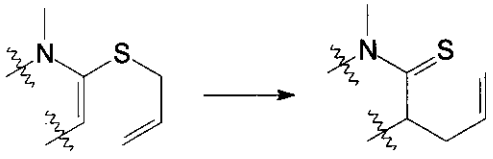
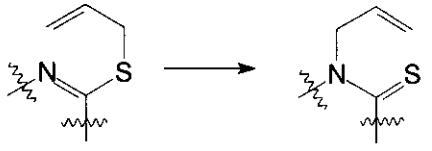
Abstract- 3-Allylthioallyl triazoles (**5**) rearrange to *N*-allyl derivatives (**6**) while 3-(2-propynyl) derivatives (**2**) provide 4,5-disubstituted 2-cyanamidothiazoles (**9**) in refluxing *p*-xylene. At lower temperatures *N*-allenyl derivatives (**8**) may be isolated and converted independently to **9**. Intermediate allenes exhibit sigmatropic inversion of substituents characteristic of Claisen rearrangement.

Although thio-Claisen rearrangement[1] of ketene thioaminals (eq. 1) in alicyclic[2-6] and aromatic[7] systems is well known, the alternative thio-Claisen rearrangement of thioimidates (eq. 2) is not as well studied[8-10] and paths such as double bond isomerization and dealkylation may predominate.[11-13] Encompassed within this latter class are thio-Claisen rearrangements in *N*-heteroaromatic systems[14] such as pyrroles, imidazoles, and triazoles (as well as their benzo-fused counterparts).



(1)

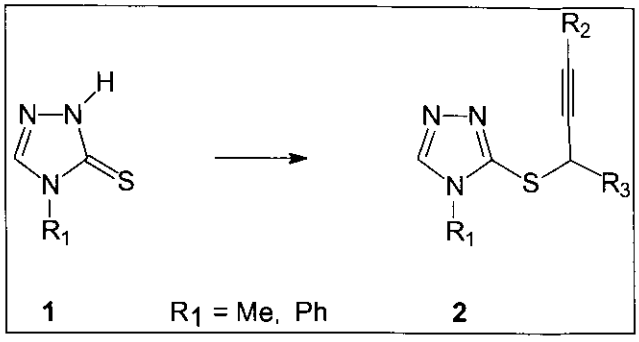


(2)

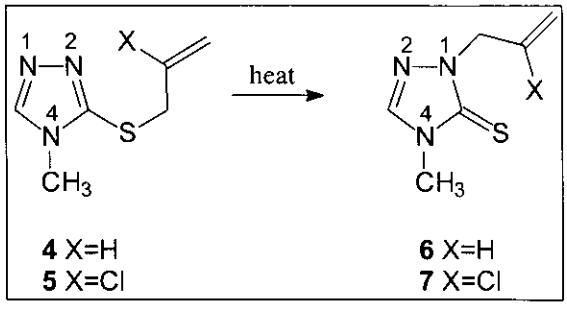
There is no literature precedence for thio-Claisen rearrangement in triazoles, but several investigators have reported acid- or base- catalyzed nonsigmatropic reactions of thioalkynyltriazoles.[15,16] In these reactions the triple bond serves merely as a carbonyl equivalent, undergoing direct cyclization with no rearrangement. Similar chemistry is observed for propynylthio-1,3,4-thiadiazoles.[17] In this communication we report substituted triazoles readily undergo thermal S→N [3,3] sigmatropic rearrangement providing a novel and synthetically useful triazole to thiazole conversion.

Simple triazoles exist as a mixture of 2*H*- and *4H*- tautomers which, in base-induced cyclizations, produce both [3,2-*b*] and [2,3-*c*] fused isomers in relative amounts which depend upon the relative basicity of the nitrogen atoms.[16d] We sought to avoid tautomeric complications in our studies by examining *N*-methyl and *N*-phenyl derivatives. Thiones (**1a,b**)[18] were readily *S*-alkylated to propargyl and substituted propargyl substrates (**2**) as well as benzyl (**3**) and allyl (**4, 5**) derivatives using standard techniques.[19]

3-Benzylthio-4-methyl-1,2,4-triazole (**3**) was recovered unchanged after several days in refluxing *p*-xylene.[20] Allyl compounds (**4**) rearranged to the *N*-allyl derivatives (**6**) in refluxing toluene (8 h), in refluxing *p*-xylene (*ca.* 1 h), or upon attempted vacuum distillation.



N- and *S*- substituted compounds are most easily differentiated in ^{1}H NMR spectra by chemical shift differences of H-5 (numbering based on **2**, **4**, or **5**): >8 ppm (typically δ 8.05- 8.15) in *S*-alkyl forms and <8 ppm (typically δ 7.75-7.85 ppm) in *N*-alkyl forms (**6**, **7**, or **8**). In ^{13}C NMR spectra both C-3 and C-5 are useful for identifying isomeric products. C-5 moved upfield upon rearrangement (δ 144-145 to δ 139-140 in thiones (**6**, **7**, or **8**)) whereas C-3 moved downfield significantly (δ 148-150 to δ 166-167 in thiones).



Refluxing the propargyl derivative (**2a**) in toluene for about 13 h (or 6 h in *p*-xylene) gave only the *N*-allenyl compound (**8**) in good yield. Refluxing other derivatives of **2** to low conversion in toluene also gave allenes as products. In cases where substitution patterns allow differentiation, evidence of sigmatropic inversion is apparent. *The most interesting observation, however, is prolonged heating of S-propargyl derivatives produces cyanoamidothiazoles in good to excellent yield* (see Table). The most easily discerned evidence for sigmatropic inversion in the N → S migration is found in these cyclized products, especially **2j** which produces **9** with the 5-ethyl-4-methyl substitution pattern. The best condition found to accomplish this conversion is to simply reflux the triazole derivative in *p*-xylene solution until the starting material disappears (usually <13 h). In all cases a single thiazole isomer was isolated.

Mechanistically, **9** may form *via* **10** (Scheme 1). Intermediates structurally similar to **10** may occur in the direct cyclization process[15,16] (R^1 must equal H, with no S → N migration and no substituent inversion) except that in all cases appearing in the literature, presumed intermediate (**10**) loses the hydrogen from N-4 to form a stable, fused thiazolotriazole. In this work, N-4 has either a methyl or phenyl substituent and the compounds follow an alternate pathway entailing scission of the triazole N-N bond with loss of a proton to form **9**.

One of the main advantages of this technique for thiazole preparation is the precise substituent placement at C-4 and C-5 with the nature of these substituents easily manipulated using readily available acetylenic precursors and simple, well established synthetic procedures.

Scheme 1

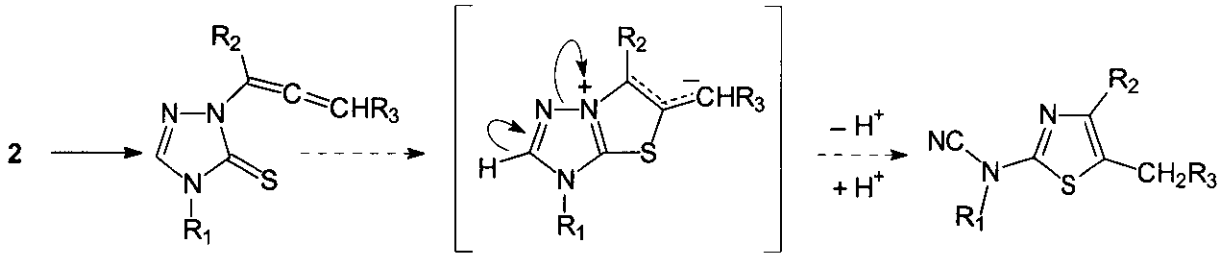


Table. Products from Thermal Rearrangement of **2**.[a]

Compound **2**	R_1	R_2	R_3	Product	Yield (%) [b]	mp (°C) of **2**	mp (°C) of product
a	Me	H	H	**8**	78	73-77.5	123-125
b	Me	Me	H	**9**	82	64-66	oil
c	Me	Me	Me	**8**[c]	72	67-70	oil
d	Me	Ph	H	**9**	76	oil	102-103
e	Me	CH_2OH	H	**9**	87	137-139	113-114
f	Me	CH_2OPh	H	**9**	65	65-66	113-114
g	Me	CH_2SPh	H	**9**	78	oil	oil
h	Ph	H	H	**8** + **9**[d]	92	114-116	-
				8[e]	89	-	127-129
i	Ph	Me	H	**9**	93	125-127	82.5-84.5
j	Ph	Me	Me	**9**	89	semisolid	-
k	Ph	Ph	H	**9**	80	117-119	145-147
l	Ph	CH_2OH	H	**9**	92	150-152	oil
m	Ph	CH_2OPh	H	**9**	90	65.5-67.5	semisolid
n	Ph	CH_2SPh	H	**9**	90	80-82	semisolid

[a] All new compounds were fully characterized by ^1H NMR, ^{13}C NMR, IR, MS, and combustion analysis.
[b] Isolated yield of product after refluxing **2** in *p*-xylene for 13 h, unless otherwise indicated. Under the same conditions, **6** and **7** are formed in 75 and 78 % yield, respectively.
[c] Formed in small quantity even after prolonged reflux in *p*-xylene (yield is based on recovered starting material).
[d] Ratio is 1:10 after 13 h reflux in *p*-xylene.
[e] Yield based on recovered starting material. The major component of the reaction is starting material (ratio of **8** to starting material is 1:9) after 13 h refluxing in toluene (and no **9** is detectable by NMR).

ACKNOWLEDGMENTS

The authors wish to thank the NSF for an equipment grant (CHE-9512445) and the Michigan Technological University Graduate School (for fellowship support to MX).

REFERENCES AND NOTES

⊥ This paper is dedicated to Professor B. S. Thyagarajan on the occasion of his 70th birthday. This work was presented in preliminary form at the 16th Int. Congress of Heterocycl. Chem., Bozeman, MT, August, 1997.

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20. Some *N*-heteroaromatic unsymmetrical dithioacetals[a] and 2-alkylthiothiazoles[b] in which no sigmatropic process is possible undergo facile S→N rearrangement. The lack of rearrangement of 3-benzylthio-4-methyl-1,2,4-triazole (**3**) under conditions leading to rearrangement of the allyl and propargyl derivatives further supports the sigmatropic nature of their reactions. (a) J.Y. Gauthier, D. Guay, D. Mayhew, N. Zajar, and R. Zamboni, *Abstr. 13th Int. Congr. Heterocycl. Chem.,* August, 1991, GE13-152; (b) ref. 19, p. 358.

Received, 2nd November, 1998