Organic LETTERS

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Regioselective Formal Hydroamination of Styrenes with 1-Phenyl-1*H*-tetrazole-5-thiol

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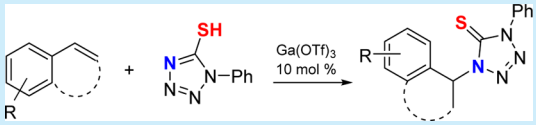
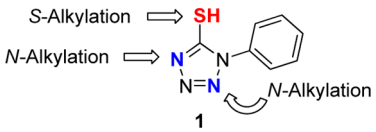
Supporting Information

ABSTRACT: 1-Phenyl-1*H*-tetrazole-5-thiol **1** (PT-thiol) is employed in a unique Markovnikov-selective formal hydroamination of styrenyl compounds in the presence of catalytic amounts of $Ga(OTf)_3$. This gives rise to the formation of tetrazolothione moieties in an atom-economical manner. Mechanistically, we have determined that this transformation may occur by kinetically favored hydrothiolation, followed by rearrangement to the observed hydroamination products.

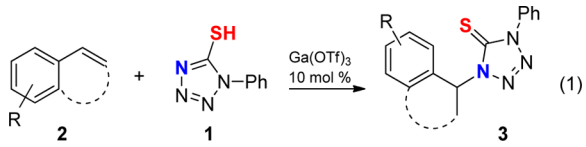


1-Phenyl-1*H*-tetrazole-5-thiol (PT-thiol) (**1**) is an intriguing molecule that exhibits ambident nucleophilic properties at sulfur and nitrogen. Kinetically controlled alkylations of **1** at sulfur are quite well-known and are often seen in the syntheses of precursors for Julia-type olefination reactions.[1−4] In contrast, examples of reactivity at nitrogen are rare[5] but tend to give thermodynamically favored products. In one such example, Vicario has shown that **1** will add to α,β-unsaturated aldehydes at nitrogen to give tetrazolothiones.[6]



Within the extensive family of nitrogen-containing heterocycles, the 1,4-disubstituted tetrazolothione has recently garnered some attention due to its biological activity in several areas of research such as pesticides and herbicides[7] and as cytotoxic agents.[8] There have also been reports that tetrazolothiones can be converted to the corresponding carbodiimides by photochemical irradiation[9−12] and into other products through reductive processes.[6] An early preparation of 1,4-disubstituted tetrazolothiones was reported by Leber in which isothiocyanates were treated with NaN_3 in EtOH and water.[13,14] This method results in low yields, requires harsh reaction conditions, and utilizes potentially explosive azides. Recently, Gyong has demonstrated a less vigorous preparation of tetrazolothiones; however, this method still requires the use of azides.[15] Another route to tetrazolothiones was reported by Rayat in which isocyanates/dichloroisocyanates are reacted with azides to furnish the desired product in 3−4 steps.[16] Others have gained access to the this heterocycle by treating the corresponding tetrazole-5-one precursor with Lawesson's reagent.[10,12,16]

In our recent publication describing the hydrothiolation of alkenes,[17] we made the cursory observation that, at elevated temperatures (i.e., 70 °C), trifluoroacetic acid (TFA) promotes the Markovnikov-selective hydroamination of a select few olefins with **1** to give tetrazolothiones. Due to the usefulness of tetrazolothiones and the synthetic limitations associated with their synthesis as outlined above, we decided to carry out a full study of this hydroamination process (eq 1).



Herein, we report an efficient formal hydroamination of styrenyl substrates with **1**, catalyzed by $Ga(OTf)_3$. We are aware of only two other Ga(III)-promoted hydroamination reactions of either alkynes or alkenes.[18,19] In these instances, the authors use $GaCl_3$ and GaI_3, which are hydrolytically unstable and therefore present some technical challenges in their usage. In contrast, our process takes advantage of $Ga(OTf)_3$, a commercially available Lewis acid that is tolerant to both moisture and air.[20−24] Two examples of the hydroamination of alkynes/alkenes catalyzed by In(III) are also known.[25,26]

After extensive optimization studies with various Lewis and Brønsted acid catalysts, we found that the best conditions are 10% $Ga(OTf)_3$ in dichloroethane (DCE) at 75 °C for 12−18 h (Table 1). Various functional groups are compatible, including esters, ethers, and halides. Interestingly, hydroamination of conjugated diene **2l** furnished a single regioisomer **3l**. Unfortunately, attempts to extend the substrate range to include other ambident sulfur/nitrogen nucleophiles such as *N*,*N*-diphenylthiourea, 1,3-oxazolidine-2-thione, or 1-*tert*-butyl-1*H*-tetrazole-5-thiol were unsuccessful, with only the latter reagent furnishing low yields of the *S*-alkylated product.

We envisioned the possibility of two distinct mechanistic pathways: (1) direct hydroamination to furnish **3a** (Scheme 1, path a) or (2) hydrothiolation followed by rearrangement

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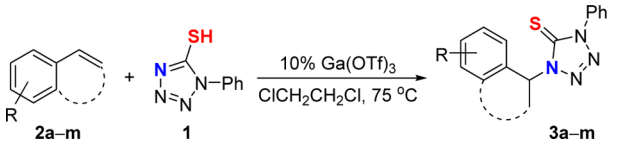
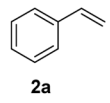
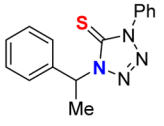
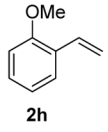
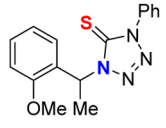
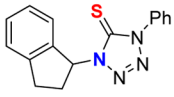
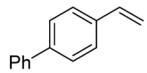
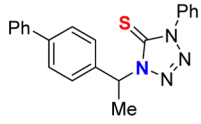
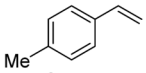
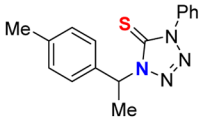
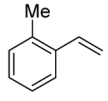
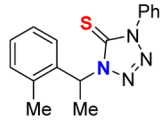
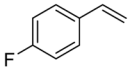
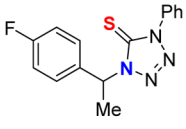
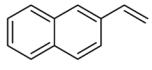
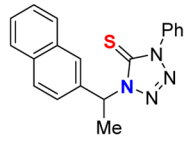
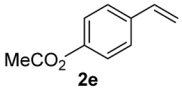
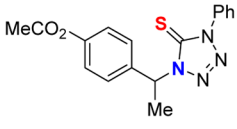
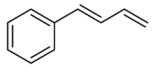
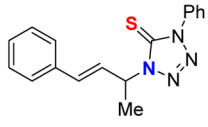
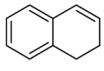
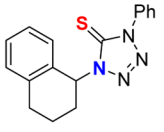
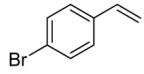
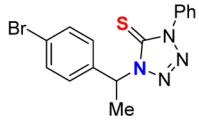
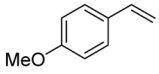
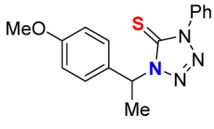
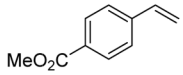
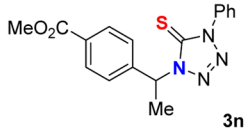
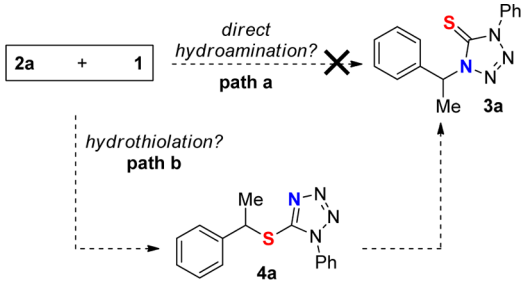
Table 1. Scope of Formal Hydroamination

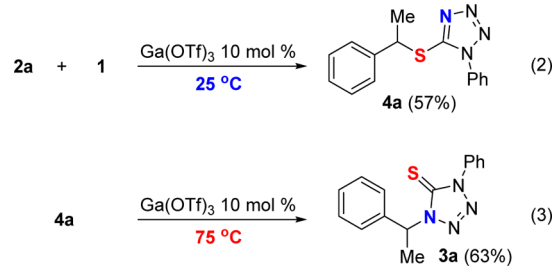


olefin	product		% yield	olefin	product		% yield
 2a		3a	70	 2h		3h	67
 2b		3b	69	 2i		3i	48
 2c		3c	75	 2j		3j	64
 2d		3d	72	 2k		3k	63
 2e		3e	50	 2l		3l	68
 2f		3f	79	 2m		3m	39
 2g		3g	77	 2n		3n	98

Scheme 1. Mechanistic Possibilities



(Scheme 1, path b). To ascertain which mechanism is operational, we first demonstrated that, at temperatures lower than that required for hydroamination (i.e., room temperature), the reaction between **1** and styrene furnished hydro*thiolation* product **4a** (eq 2). It was then confirmed that when **4a** was subjected to typical hydroamination conditions [10 mol % $Ga(OTf)_3$ at 75 °C], rearrangement to **3a** occurred in good yield (eq 3). These data support pathway **b**, in which hydrothiolation occurs first and is then followed by rearrangement to give **3a**.



We also prepared enantioenriched thioether (*R*)-**4a** (99% ee) by means of Mitsunobu inversion between **1** and (*S*)-phenethyl alcohol. (*R*)-**4a** was subjected to hydroamination conditions, and the reaction was halted at partial conversion (55% **3a** and 45% **4a** isolated yields). We then determined the enantiopurity

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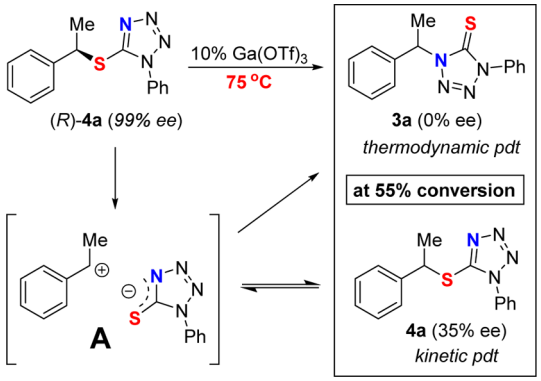
of **4a** to be 35% ee and that of rearranged product **3a** to be 0% ee (Scheme 2). The low residual enantiomeric excess of **4a** can

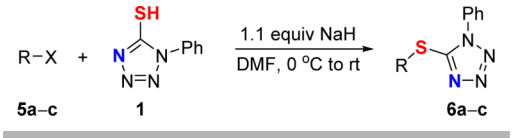
Scheme 2. Rearrangement of Enantioenriched (*R*)-4a to 3a

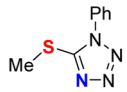
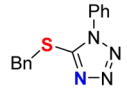
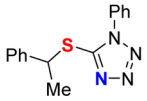


be rationalized if one considers that $Ga(OTf)_3$ likely facilitates ionization of (*R*)-**4a** to generate ion pair **A** in which the original stereochemical information has been deleted. Alkylation at sulfur occurs reversibly to give kinetic product **4a**. Eventually, alkylation at nitrogen ensues to yield the racemized, but thermodynamically preferred, hydroamination product **3a**.

We then showed that *N*-alkylation products are, in fact, not accessible when **1** is reacted with alkyl halides under typical base-mediated protocols. When **1** was treated with NaH in the presence of alkyl halides **5a–c**, we found that alkylation occurs exclusively at sulfur in excellent yields (Table 2). These results

Table 2. PT-thiol Alkylation at Sulfur



alkyl halide		product		% yield
5a	MeI	**6a**		quant
5b	BnBr	**6b**		quant
5c		**6c**		97

underscore the complementary nature of our hydroamination process as compared to alkylation of **1** with halide-based electrophiles.

In summary, we have demonstrated the feasibility of carrying out formal hydroamination reactions between styrenes and **1** under $Ga(OTf)_3$ catalysis. The resulting tetrazoline-5-thione is a unique heterocyclic scaffold that is of interest for its demonstrated biological and insecticidal activity. We have also elucidated a probable mechanistic pathway in which we show that the reaction likely proceeds through a kinetically favored hydrothiolation event, which then undergoes rearrangement to the thermodynamically preferred formal hydroamination products.

■ ASSOCIATED CONTENT

Supporting Information

Contains experimental and compound characterization details and copies of spectra of isolated products. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morley, A. *Synlett* **1998**, 26.
(2) Blakemore, P. R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2563.
(3) Pan, X.; Curran, D. P. *Org. Lett.* **2014**, *16*, 2728.
(4) Han, X.; Wu, J. *Org. Lett.* **2010**, *12*, 5780.
(5) Stefan, E.; Nalin, A. P.; Taylor, R. E. *Tetrahedron* **2013**, *69*, 7706.
(6) Uria, U.; Reyes, E.; Vicario, J. L.; Badía, D.; Carrillo, L. *Org. Lett.* **2011**, *13*, 336.
(7) Foldenyi, R. *Monatsh. Chem.* **1995**, *126*, 1035.
(8) Gundugola, A. S.; Chandra, K. L.; Perchellet, E. M.; Waters, A. M.; Perchellet, J.-P. H.; Rayat, S. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 3920.
(9) Quast, H.; Nahr, U. *Chem. Ber.* **1983**, *116*, 3427.
(10) Quast, H.; Nahr, U. *Chem. Ber.* **1985**, *118*, 526.
(11) Dunkin, I. R.; Shields, C. J. *Tetrahedron* **1989**, *45*, 259.
(12) Alawode, O. E.; Robinson, C.; Rayat, S. *J. Org. Chem.* **2011**, *76*, 216.
(13) Lieber, E.; Pillai, C. N.; Hites, R. D. *Can. J. Chem.* **1957**, *35*, 832.
(14) Lieber, E.; Ramachandran, J. *Can. J. Chem.* **1959**, *37*, 101.
(15) Han, S.-Y.; Lee, J.-W.; Kim, H.-J.; Kim, Y.-J.; Lee, S.-W.; Gyoung, Y.-S. *Bull. Korean Chem. Soc.* **2012**, *33*, 55.
(16) Rayat, S.; Chhabra, R.; Alawode, O.; Gundugola, A. S. *J. Mol. Struct.* **2009**, *933*, 38.
(17) Savolainen, M. A.; Wu, J. *Org. Lett.* **2013**, *15*, 3802.
(18) Li, L.; Huang, G.; Chen, Z.; Liu, W.; Wang, X.; Chen, Y.; Yang, L.; Li, W.; Li, Y. *Eur. J. Org. Chem.* **2012**, 5564.
(19) Jaspers, D.; Kubiak, R.; Doye, S. *Synlett* **2010**, 1268.
(20) Olah, G. A.; Farooq, O.; Farnia, S. M. F.; Olah, J. A. *J. Am. Chem. Soc.* **1988**, *110*, 2560.
(21) Prakash, G. K. S.; Yan, P.; Bucsi, I.; Tanaka, M.; Olah, G. A. *Catal. Lett.* **2003**, *85*, 1.
(22) Yan, P.; Batamack, P.; Surya Prakash, G. K.; Olah, G. A. *Catal. Lett.* **2005**, *103*, 165.
(23) Prakash, G. K. S.; Mathew, T.; Panja, C.; Vaghoo, H.; Venkataraman, K.; Olah, G. A. *Org. Lett.* **2007**, *9*, 179.
(24) Prakash, G. K. S.; Mathew, T.; Olah, G. A. *Acc. Chem. Res.* **2012**, *45*, 565.
(25) Huang, J.-M.; Wong, C.-M.; Xu, F.-X.; Loh, T.-P. *Tetrahedron Lett.* **2007**, *48*, 3375.
(26) Sarma, R.; Prajapati, D. *Chem. Commun.* **2011**, *47*, 9525.

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