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# Non-catalyzed addition of heterocyclic thiols and 5-substituted-1*H*-tetrazoles to vinyl ethers

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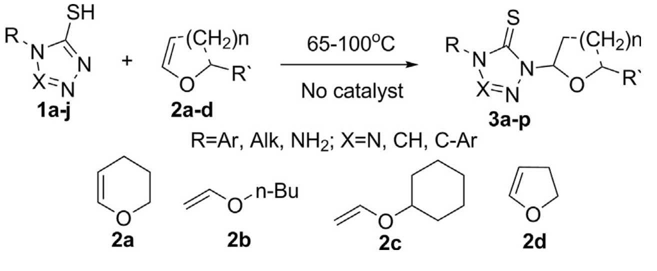
## ABSTRACT

The alkylation of 1-substituted 1*H*-tetrazole-5-thiols and 4-substituted 4 H-1,2,4-triazole-3-thiols with alkyl halides or sulfonates lead to the formation of S-alkylated products regardless of the substituent on the heterocycle. In this work, we found that substituted 1*H*-tetrazole-5-thiols and 4 H-1,2,4-triazole-3-thiols readily reacted with vinyl ethers in the absence of a catalyst to exclusively form *N*-substituted 1*H*-tetrazole-5(4*H*)-thiones and 1*H*-1,2,4-triazole-5(4*H*)-thiones, respectively. Furthermore, the reactions of 5-substituted-1*H*-tetrazoles with vinyl ethers under the same conditions selectively yielded 2,5-disubstitued tetrazoles.

The direct addition of SH or NH functional groups across a carbon-carbon π bond is one of the most effective methods for their functionalization.[1] Such reactions have attracted attention due to good atom economy, high efficiency, and high selectivity. One of the synthetic applications of these reactions is the protection of alcohols, thiols and amines with vinyl ethers, for example, with 3,4-dihydro-2*H*-pyran, to form tetrahydropyranyl derivatives.[2] These derivatives are stable to basic conditions, organolithium and Grignard reagents, Red-Al®, lithium aluminum hydride, acetic anhydride, and chromium trioxide oxidation yet are easily cleaved by dilute acids to regenerate the original functional group. In general, Brønsted acids[3] or Lewis acids[4] are used to catalyze the addition of aliphatic and aromatic alcohols, thiols and amines to the double bond of vinyl ethers. Recently, it was shown that mixed thioacetals could also be prepared from thiols and vinyl ethers in the presence of $Pd(OAc)_2$ (5 mol%).[5] However, the addition of acidic NH heterocycles and heterocyclic thiols to vinyl ethers is not well studied. Information on similar reactions is limited to a few examples in which the addition of vinyl ethers to triazoles under various conditions is described.[6] We have found that the addition of acidic heterocyclic thiols and NH heterocycles to vinyl ethers proceeds with excellent regioselectivity to afford the corresponding Markovnikov adducts in good yield, which may open up a new protection strategy for these substrates.

First, we optimized the addition of 1-phenyl-tetrazole-5-thiol **1a** to 3,4-dihydro-2*H*-pyran **2a** without any catalyst. We found that tetrazole-5-thiol **1a** was highly reactive under these conditions (Scheme 1). Initially, the reaction of **1a** with 3,4-dihydro-2*H*-pyran **2a** in THF was carried out at 40 °C, but the reaction rate at this temperature was quite low. However, at 65 °C, the reaction was complete in 2 h, and compound **3a** was isolated in quantitative yield (Table 1, entry 1). In the case of 4-methyl-4*H*-1,2,4-triazole-3-thiol **1h**, after 8 h at 65 °C, no reaction with **2a** was observed. Full conversion of triazole **1h** to the protected derivative **3l** could only be achieved after 24 h at 100 °C in 1,4-dioxane (Table 1, entry 12).



**Scheme 1.** Addition of vinyl ethers to heterocyclic thiols.

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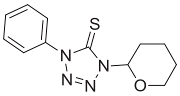
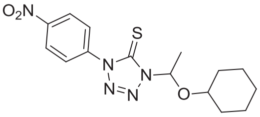
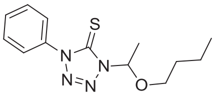
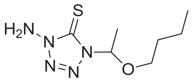
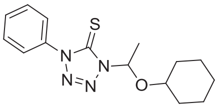
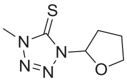
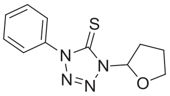
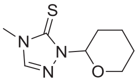
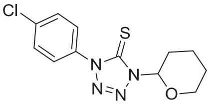
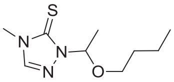
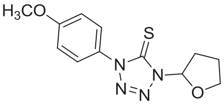
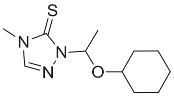
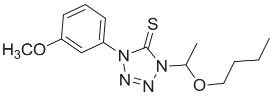
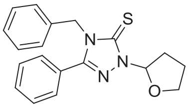
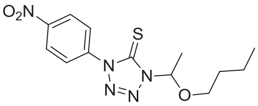
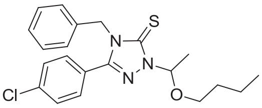
**Table 1**
Addition of vinyl ethers to heterocyclic thiols.[a]

| Entry | R/X | Vinyl ether | Product (Isolated yield) | Entry | R/X | Vinyl ether | Product (Isolated yield) |
|---|---|---|---|---|---|---|---|
| 1 | Ph/N<br>**1a** | **2a** | <br>**3a** (98%) | 9 | 4-NO$_2$-Ph/N<br>**1e** | **2c** | <br>**3i** (62%) |
| 2 | Ph/N<br>**1a** | **2b** | <br>**3b** (72%) | 10 | NH$_2$/N<br>**1f** | **2b** | <br>**3j** (82%) |
| 3 | Ph/N<br>**1a** | **2c** | <br>**3c** (80%) | 11 | Me/N<br>**1g** | **2d** | <br>**3k** (99%) |
| 4 | Ph/N<br>**1a** | **2d** | <br>**3d** (99%) | 12 | Me/CH<br>**1h** | **2a** | <br>**3l** (91%) |
| 5 | 4-Cl-Ph/N<br>**1b** | **2a** | <br>**3e** (95%) | 13 | Me/CH<br>**1h** | **2b** | <br>**3m** (86%) |
| 6 | 4-MeO-Ph/N<br>**1c** | **2d** | <br>**3f** (99%) | 14 | Me/CH<br>**1h** | **2c** | <br>**3n** (91%) |
| 7 | 3-MeO-Ph/N<br>**1d** | **2b** | <br>**3g** (95%) | 15 | Bn/Ph-C<br>**1i** | **2d** | <br>**3o** (80%) |
| 8 | 4-NO$_2$-Ph/N<br>**1e** | **2b** | <br>**3h** (68%) | 16 | Bn/4-Cl-Ph-C<br>**1j** | **2b** | <br>**3p** (88%) |

[a] Reagents and conditions: entries 1–11; 1-substituted-1*H*-tetrazole-5-thiol **1a–g** (1 mmol), vinyl ether **2a–d** (3 mmol) THF (5 mL), 65 °C, 2 h; entries 12–16; 1,2,4-triazole-3-thiol **1h–j** (1 mmol), vinyl ether **2a–d** (3 mmol), 1,4-dioxane (5 mL), 100 °C, 24 h.

It was also found that no reaction occurred between 3,4-dihydro-2*H*-pyran **2a** and 1-methylimidazole-2-thiol or benzimidazole-2-thiol, even at 100 °C.

Next, the addition of vinyl ethers **2a–d** to substituted tetrazole-5-thiols **1a–g** and 1,2,4-triazole-3-thiols **1h–j** (Scheme 1) was examined, and the results are summarized in Table 1.[7] Substituents on the tetrazole and triazole rings had little effect on the isolated yields of the products. Most products were cleanly isolated by the evaporation of the volatiles from the reaction mixture. Oily products were purified by column chromatography. All of the tested tetrazole-5-thiols **1a–g** (Table 1, entry 1–11) and 1,2,4-triazole-3-thiols **1h–j** (Table 1, entry 12–16) gave good to excellent yields of the addition products.

The abovementioned reactions can afford nitrogen or sulfur substituted products. An advanced $^{1}H–^{15}N$ gHMBC experiment was used to unambiguously assign the proton signals. The correlation of the hydrogen atoms of the OCH groups of tetrazole **3a** (dd, 5.84 ppm) and triazole **3l** (dd, 5.74 ppm) with the nitrogen atoms was clearly observed, which would not be possible if substitution had occurred on the sulfur atom. Thus, both the tetrazole and triazole scaffolds showed clear correlations across three bonds from the tetrahydropyranyl OCH group to the nitrogen atom. These observations confirm *N*-substitution of the products (see ESI).

As noted above, Brønsted acids are used to catalyze the addition of aliphatic and aromatic thiols to the double bond of vinyl ethers, in particular of 3,4-dihydro-2*H*-pyran **2a**. The addition of 1-substituted 1*H*-tetrazole-5-thiols **1a–g** and 4-substituted 4*H*-1,2,4-triazole-3-thiols **1h–j** to vinyl ethers is probably enhanced by their acidic properties. The proposed mechanism for the addition is depicted in Scheme 2.

In accordance with the proposed mechanism, the difference in the reactivity of the heterocyclic thiols can easily be explained by differences in the p$K_a$ values of the substrates. For example, the p$K_a$ of 1-phenyl-1*H*-tetrazole-5-thiol **1a** is 3.65,[8] the p$K_a$ of 4-methyl-4*H*-1,2,4-triazole-3-thiol **1h** is 8.02,[9] the p$K_a$ of 1-methylimidazole-2-thiol is 11.38,[10] and the p$K_a$ of benzimidazole-2-thiol is 10.55.[11] Furthermore, the addition of TsOH (5 mol %) also catalyzed the reaction of 1-phenyl-1*H*-tetrazole-5-thiol **1a** with 3,4-dihydro-2*H*-pyran **2a**, and the reaction was finished in 2 h at rt. It should be noted that the acid catalyzed addition of alkenes to 1-substituted-1*H*-tetrazole-5-thiols also gave *N*-substituted tetrazole-5-thiones.[12]