Tetrahedron Letters 59 (2018) 1112–1115

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

# Understanding the tetrazole ring cleavage reaction with hydrazines: Structural determination and mechanistic insight

Olga Ya. Shyyka [a,*], Nazariy T. Pokhodylo [a], Yurii I. Slyvka [b], Evgeny A. Goreshnik [c], Mykola D. Obushak [a]

[a] Department of Organic Chemistry, Ivan Franko National University of Lviv, Kyryla i Mefodiya St. 6, Lviv 79005, Ukraine
[b] Department of Inorganic Chemistry, Ivan Franko National University of Lviv, Kyryla i Mefodiya St. 6, Lviv 79005, Ukraine
[c] Department of Inorganic Chemistry and Technology, Jožef Stefan Institute, Jamova 39, SI-1000 Ljubljana, Slovenia

ARTICLE INFO

*Article history:*
Received 10 December 2017
Revised 1 February 2018
Accepted 6 February 2018
Available online 7 February 2018

*Keywords:*
1*H*-Tetrazole
Hydrazines
Thieno[2,3-*d*]pyrimidin-4(3*H*)-ones
Thieno[3,2-*d*]pyrimidin-4(3*H*)-ones
[1]Benzofuro[3,2-*d*]pyrimidin-4(3*H*)-one
Regioselectivity

ABSTRACT

A distinction in the behaviour of several hydrazines as *N*-nucleophiles in the recently developed one-pot method for pyrimidine core annulation *via* 1*H*-tetrazole ring cleavage was examined. The product structures, 2,3-diamino- or hydrazino derivatives of thieno[3,2-*d*]pyrimidin-4(3*H*)-ones, thieno[2,3-*d*]pyrimidin-4(3*H*)-ones and [1]benzofuro[3,2-*d*]pyrimidin-4(3*H*)-one, were elucidated based on NMR and single crystal X-ray analysis.



Substituted 1*H*-tetrazoles are considered to be versatile synthetic building blocks, possessing —N=N— double bonds with a particular ability to eliminate nitrogen and thus generate reactive species.[1–4] Previously, these compounds have been demonstrated to be suitable precursors for the construction of nitrogen-containing heterocycles, such as thienopyrimidines,[4–6] which are well-known for their wide array of pharmacological activities especially in cancer and antivirus research.[7,8]

Therefore, the reactivity investigation of functionalized thiophenes bearing a 1*H*-tetrazole ring is an interesting area of research for the development of convenient approaches towards novel thienopyrimidine derivatives.

Recently, we reported that alkyl 2-(1*H*-tetrazol-1-yl)-4-$R^1$-5-$R^2$-thiophene-3-carboxylates, obtained from alkyl 2-amino-thiophene-3-carboxylates, undergo recyclization *via* cleavage of the tetrazole ring, elimination of nitrogen, and annulation of the pyrimidinone core (Fig. 1).[5,6] This simple one-pot reaction accommodates many different basic amines and hydrazines and proceeds in high yield under mild conditions, with exclusive regioselectivity observed for a number of aliphatic amines.[6]

As a continuation of our work, the reactions of a number of hydrazines with 1*H*-tetrazoles were examined in order to better understand the nature of pyrimidine formation.

The one-pot solvent-free reaction of tetrazoles **2a–d**[12] with hydrazine hydrate **3a** for 5–15 min at reflux afforded 2,3-diaminothieno[3,2-*d*]pyrimidin-4(3*H*)-ones **4a–c** and [1]benzofuro[3,2-*d*]pyrimidin-4(3*H*)-one **4d** in excellent yields (Table 1, entries 1–5).[13] It should be noted that decreasing the reaction time allowed the desired fused pyrimidines to be obtained in higher yields in comparison to the previous study.[5]

Next, the reaction direction depending on the nature of the hydrazine was investigated. It is clear that the nitrogen atoms in monosubstituted hydrazines have different nucleophilicity and the formation of a mixture of products is possible.

Therefore, methylhydrazine **3b** and phenylhydrazine **3c** were also studied. Novel thieno[2,3-*d*]pyrimidin-4(3*H*)-ones **4f–h** were obtained in high yields *via* the reaction of 1*H*-tetrazoles **2f–h** with methylhydrazine **3b** (Table 1, entries 6–9).[13]

Conversely, treatment of 1*H*-tetrazoles **2f–h** with phenylhydrazine **3c** did not result in formation of the desired thienopyrimidine. The extended reaction time and higher temperatures led to decomposition of compounds.

In our previous work, the isomeric 2,3-diaminothieno[2,3-*d*]pyrimidin-4(3*H*)-one (Table 1, entry 5) was described,[5] however, single crystal X-ray analysis was not performed. In this case,

* Corresponding author.
*E-mail addresses:* shiyka.olya@gmail.com, olga.shyyka@lnu.edu.ua (O.Ya. Shyyka).

https://doi.org/10.1016/j.tetlet.2018.02.016
0040-4039/

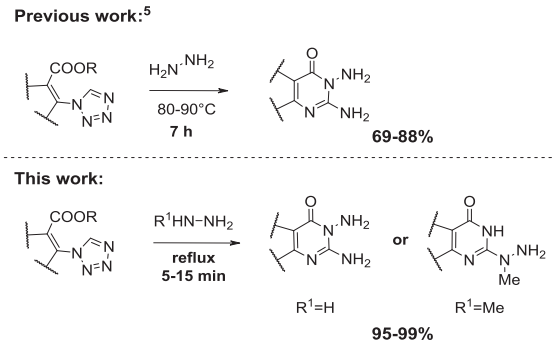
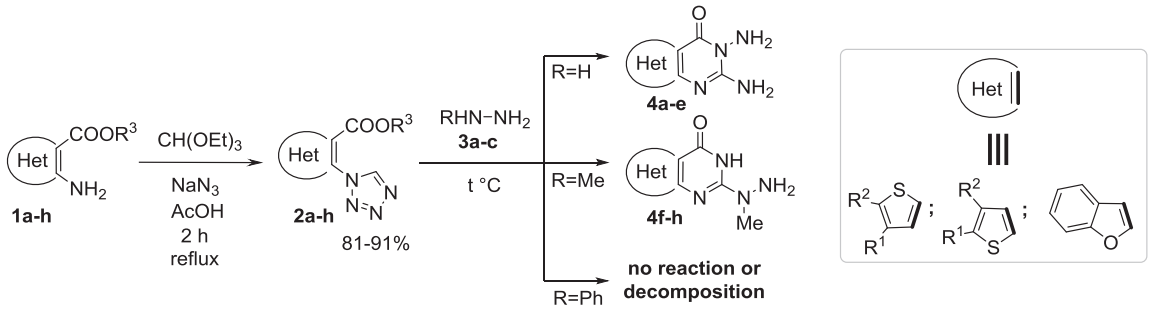


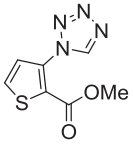
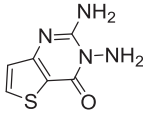
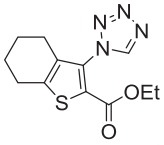
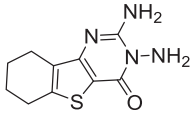
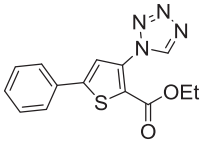
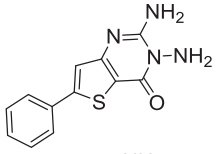
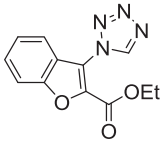
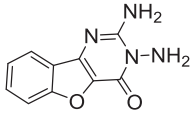
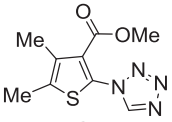
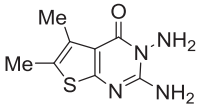
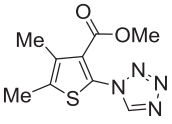
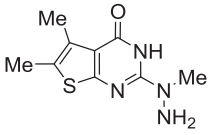

**Fig. 1.** Pyrimidine annulation *via* tetrazole ring cleavage with hydrazines.

X-ray structural determination of the previously described 2,3-diamino-5,6-dimethylthieno[2,3-*d*]pyrimidin-4(3*H*)-one **4e** (Fig. 2a) and 2-(1-methylhydrazino)-5,6,7,8-tetrahydro[1] benzothieno[2,3-*d*]pyrimidin-4(3*H*)-one **4g** (Fig. 2b) confirmed the assigned product structures (detailed information with Hirshfeld surface studies is provided in the ESI).

Previously a strong correlation between the basicity and nucleophilicity of the involved reactants was demonstrated.[6] The target thienopyrimidines were easily prepared in excellent yield using basic nucleophilic amine reagents. In contrast, weakly basic amines (pKa <6) were unreactive in this protocol. Such a statement implicitly explains the reactivity in the described reaction of tetrazoles with hydrazines. Hydrazine hydrate and methylhydrazine are examples of good bases and good nucleophiles (pKa 8.07 and

**Table 1**
Synthesis of thieno[3,2-*d*]pyrimidin-4(3*H*)-ones **4a**–**c**, thieno[2,3-*d*]pyrimidin-4(3*H*)-ones **4e**–**h** and [1]benzofuro[3,2-*d*]pyrimidin-4(3*H*)-one **4d** *via* the reaction of 1*H*-tetrazoles **2a**–**h** with hydrazines **3a**–**c**.




| Entry | Tetrazole | | Hydrazine | | Time | Product | | m.p. °C | Yield (%) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | **2a** |  | **3a** | $H_2NNH_2$ | 15 min | **4a** |  | >300 | 99 |
| 2 | **2b** |  | **3a** | $H_2NNH_2$ | 5 min | **4b** |  | >300 | 98 |
| 3 | **2c** |  | **3a** | $H_2NNH_2$ | 7 min | **4c** |  | >300 | 95 |
| 4 | **2d** |  | **3a** | $H_2NNH_2$ | 5 min | **4d** |  | 287 (dec.) | 98 |
| 5 | **2e** |  | **3a** | $H_2NNH_2$ | 7 min | **4e**[a] |  | 285–286 | 97 |
| 6 | **2f** |  | **3b** | $MeNHNH_2$ | 7 min | **4f** |  | 238–239 | 98 |

(*continued on next page*)