Tetrahedron Letters xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Synthesis of novel 1,2,4-trizaole- and isoxazol(in)e-containing heterocycles

Alicia K. Franzen, William J. Marshall, Kyung-Ho Park *

DuPont Central Research and Development, E. I. duPont de Nemours and Company, Experimental Station, PO Box 8352, Wilmington, DE 19880, United States

ARTICLE INFO

Article history:
Received 12 May 2016
Revised 7 June 2016
Accepted 8 June 2016
Available online xxxx

Keywords:
Triazole
Isoxazole
Isoxazoline
Aldoxime, nitrile oxide
1,3-Dipolar cycloaddition
Annulated ring system

ABSTRACT

A route for the regiospecific synthesis of 3-(triazol-3-yl)-1,2-isoxazol(in)e-5-yl-aryl derivatives has been developed by intermolecular 1,3-dipolar cycloaddition chemistry, and novel annulated compounds having triazole/isoxazole have been prepared by employing intramolecular nitrile oxide 1,3-dipolar cycloaddition.

The triazole heterocycle has played an important role in agrochemical[1] and medicinal[2] applications. Similarly, the isoxazol(in)e[3] moiety has been employed extensively to modulate the biological activity of various other motifs, including triazoles. Thus, isoxazole-containing triazoles have been prepared previously by several groups for biological evaluation.[4] For example, as shown in Scheme 1, 4-(triazol-5-yl)-1,2-isoxazol-5-yl-aryl derivatives **1**[5] have been prepared using triazole and methyl benzoate derivatives as starting materials. The heterocycle isoxazole was introduced in the last step via replacement of dimethyl amine with hydroxylamine, followed by ring closure. The resulting class of isoxazole-containing triazoles exhibited insecticidal and acaricidal activities.

As part of our efforts in the preparation and biological evaluation of novel heterocycles containing both triazoles and isoxazol(in)es, we were interested in the triazole/isoxazole regioisomer of **1**, and disclose herein a useful route for the synthesis of 3-(triazol-3-yl)-1,2-isoxazol-5-yl-aryl derivatives **2**. Furthermore, **2** can introduce additional molecular diversity at the 4-position of the isoxazole via bromination followed by Suzuki cross-coupling.[6] The 3-position of the isoxazole in **1** is inert to halogenation and therefore is unable to undergo a similar type of transformation (Fig. 1).

A retrosynthetic analysis of the targeted structure **2** is shown in Scheme 2. The desired isoxazole can be obtained via the nitrile oxide 1,3-dipolar cycloaddition reaction[7] of key intermediate aldoxime **3** with alkyne derivatives. 1,2,4-Triazoles functionalized with aldoxime at the 5-position are typically prepared from the corresponding aldehydes **4**, which are synthesized by oxidation of the alcohol[8] derived from the starting triazole **5**.

As depicted in Scheme 3, our initial attempts to prepare aldehyde **10** included the oxidation of primary alcohol **9**, which can be obtained from the reduction of the corresponding acid **8**. To prepare this acid, triazole **6**[9] was treated with *n*-BuLi followed by carbon dioxide at −78 °C to afford lithium carboxylate **7**. However, upon neutralization of this lithium salt using hydrochloric acid, the resultant acid **8** proved unstable, losing carbon dioxide and reverting back to the starting material **6** in almost quantitative yield. Even in the absence of HCl, it was observed that the isolated solid lithium salt **7** slowly converted back to the starting material **6** due to moisture sensitivity.

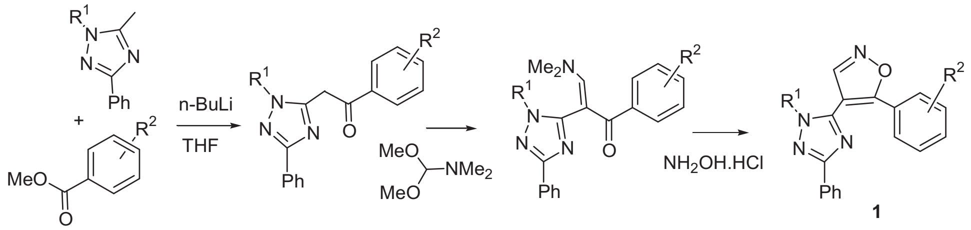
To avoid undesirable decarboxylation, the lithium salt **7** was neither acidified nor isolated. Instead, in situ methylation was employed to afford the stable methyl ester **11**. The desired formyl-substituted triazole **10** was then obtained via reduction of **11** with LAH to afford alcohol **9**, followed by Swern oxidation (Scheme 4).

---

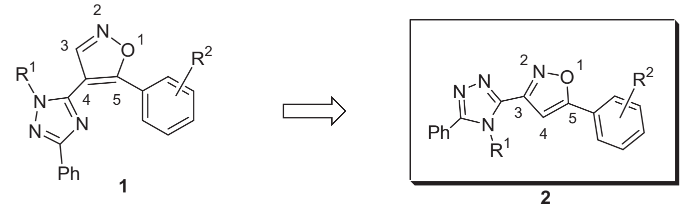
* Corresponding author. Tel.: +1 302 529 5887.
E-mail address: kyunghopark19@hotmail.com (K.-H. Park).

http://dx.doi.org/10.1016/j.tetlet.2016.06.034
0040-4039/© 2016 Elsevier Ltd. All rights reserved.

Please cite this article in press as: Franzen, A. K.; et al. *Tetrahedron Lett.* (2016), http://dx.doi.org/10.1016/j.tetlet.2016.06.034



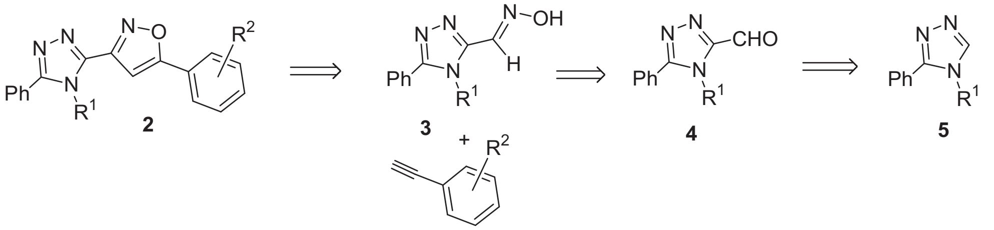
Scheme 1. Route to 4-(triazol-5-yl)-1,2-isoxazol-5-yl-aryl derivatives.



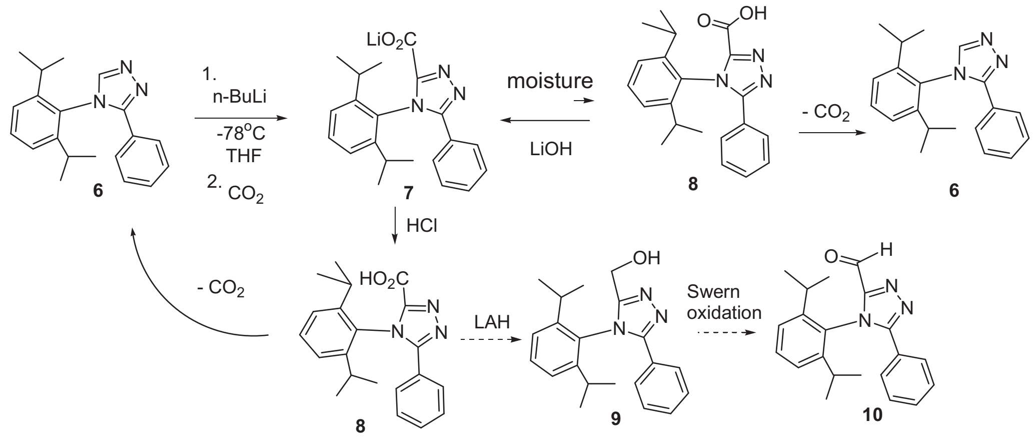
4-(Triazol-5-yl)-1,2-isoxazol-5-yl-aryl

3-(Triazol-3-yl)-1,2-isoxazol(in)-5-yl-aryl

Figure 1. Regioisomer **2** (triazol-3-yl & 3,5-disubstituted isoxazole), compared with **1** (triazol-5-yl & 4,5-disubstituted isoxazole).



Scheme 2. Retrosynthetic analysis of targeted structure **2**.



Scheme 3. Attempt to introduce an aldehyde functional group at the 5-position of 1,2,4-triazole.

Subsequently, a much more straightforward protocol[10] employing n-BuLi/DMF was applied to introduce the formyl group at the triazole 5-position. Thus, triazole **6-a**[11] was converted to **10-a** in a single step in 75% yield. Reaction of the aldehyde-containing triazoles **10** and **10-a** with hydroxylamine and triethylamine afforded the corresponding precursor aldoximes **12** and **12-a** in good yield. Utilizing the Husigen method,[7] nitrile oxide **13** was generated in situ in the presence of bleach; this allowed for 1,3-dipolar cycloadditions to be carried out with several dipolarophiles, providing **15** (e.g., the targeted regioisomer **2**), along with its isoxazoline derivative **16** (Scheme 5, Table 1). To reduce the amount of dimerized adduct **14**, an excess of dipolarophile (10 equiv) was used at room temperature.

Due to the dominance of steric over electronic effects, nitrile oxides generally undergo 1,3-dipolar cycloaddition reactions with terminal alkynes or alkenes to afford 3,5-disubsituted isoxazoles or isoxazolines, respectively, as the major regioisomers. It has been previously reported that exclusive formation of 3,5-disubstituted isoxazoles can be achieved via copper(I)-catalyzed 1,3-dipolar cycloaddition to terminal alkynes.[12] On the other hand,

Please cite this article in press as: Franzen, A. K.; et al. *Tetrahedron Lett.* (2016), http://dx.doi.org/10.1016/j.tetlet.2016.06.034