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

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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).

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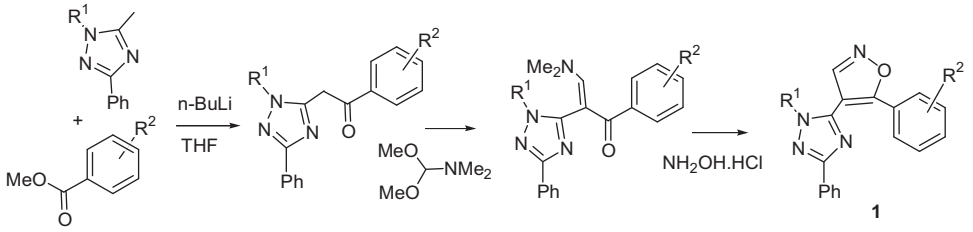


Scheme 1. Route to 4-(triazol-5-yl)-1,2-isoxazol-5-yl-aryl derivatives.

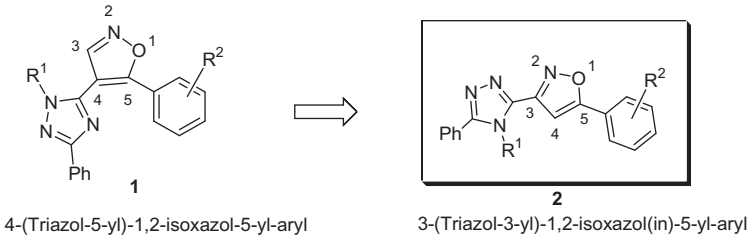
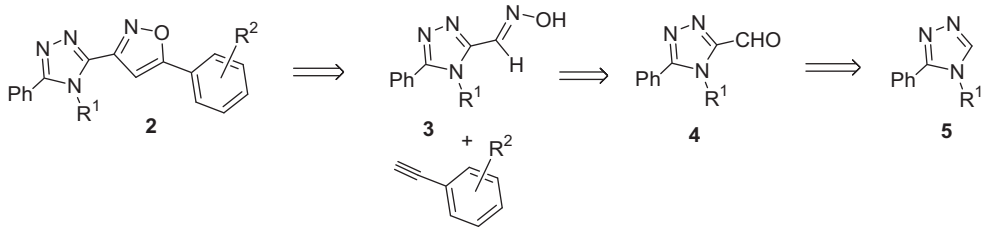
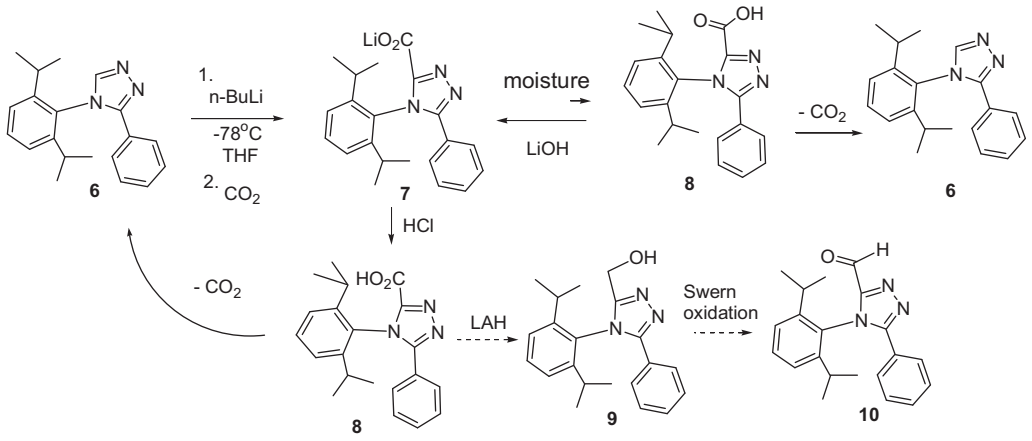


Figure 1. Regioisomer **2** (triazol-3-yl & 3,5-disubstituted isoxazole), compared with **1** (triazol-5-yl & 4,5-disubstituted isoxazole).



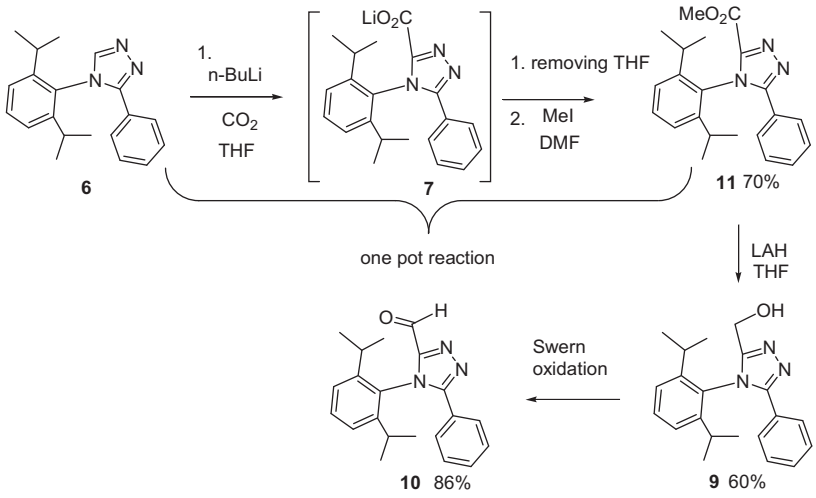
Scheme 2. Retrosynthetic analysis of targeted structure **2**.



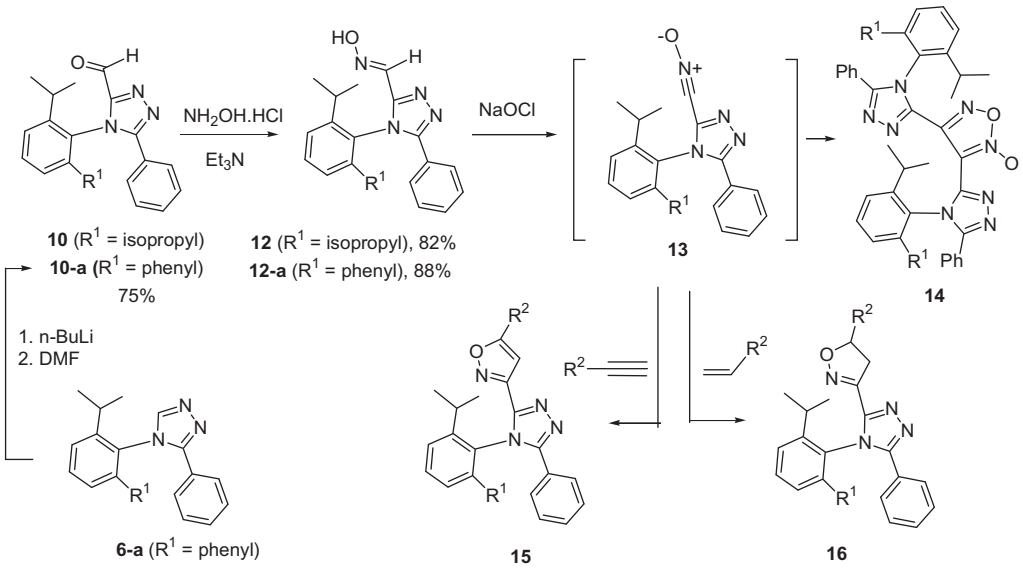
Scheme 3. Attempt to introduce an aldehyde functional group at the 5-position of 1,2,4-triazole.

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,



Scheme 4. Preparation of triazole **10** functionalized with a formyl group at the 5-position.



Scheme 5. Route to 3-(triazol-3-yl)-1,2-isoxazol(in)-5-yl-aryl derivatives **15** and **16**.

Table 1
3-(Triazol-3-yl)-1,2-isoxazol(in)-5-yl-aryl derivatives **15** and **16**

Compound	R^1	R^2	Yield[a] (%)
15-a	Isopropyl	Ph	67
15-b	Isopropyl	3-Pyridyl	68
15-c	Isopropyl	2-F-Ph	64
15-d	Isopropyl	2-Pyridyl	70
15-e	Ph	4-NC-Ph	66
15-f	Ph	4-*N*,*N*-Dimethyl-Ph	69
15-g	Ph	3-MeO-Ph	80
15-h	Ph	Biphenyl	72
16	Isopropyl	Ph	89

[a] Isolated yield.

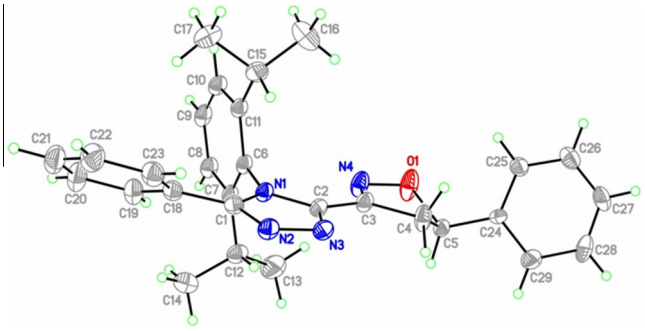
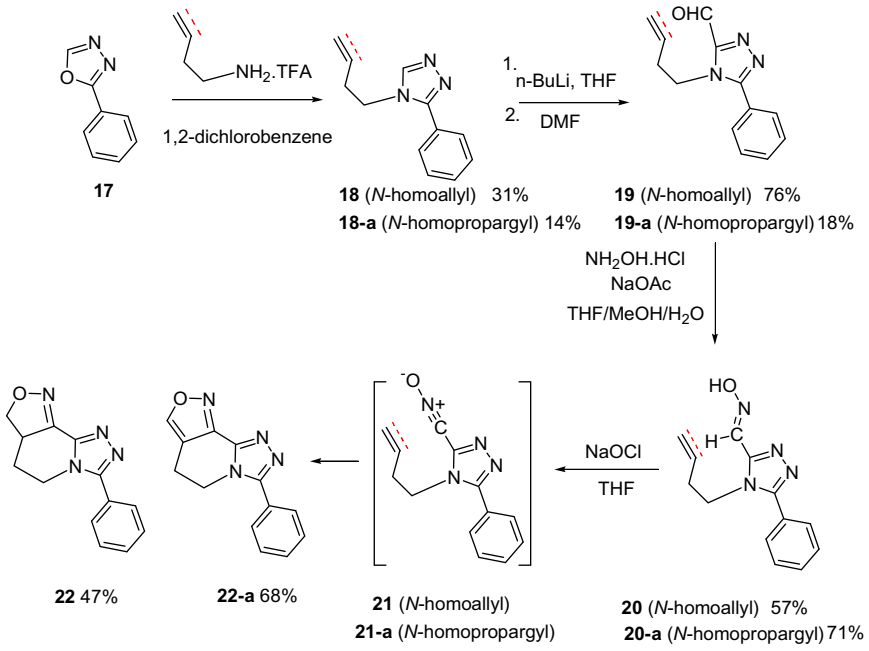


Figure 2. X-ray structure of 3,5-disubstitued isoxazoline (compound **16**).

3,4-disubstituted isoxazoles are formed as the major regioisomers in ruthenium(II)-catalyzed 1,3-dipolar cycloadditions.[13] In our synthesis, even without the aforementioned Cu(I) catalyst, 3,5-disubstituted regioisomers were observed exclusively. The connectivity of compound **16** was confirmed via X-ray crystallography (Fig. 2).[17]

With this 1,3-dipolar cycloaddition methodology in hand, we undertook the construction of novel annulated ring systems containing both isoxazol(in)e and triazole moieties tethered together about a central pyridine-derived core. As illustrated in Scheme 6,



Scheme 6. Route to novel annulated ring systems **22** and **22-a** containing both isoxazol(in)e and triazole tethered together about a central pyridine-derived core.

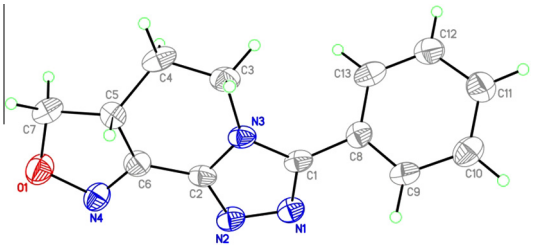


Figure 3. X-ray structure of annulated heterocycle (compound **22**) containing both isoxazoline and triazole about a central pyridine-derived core.

we designed the synthetic route to the fused heterocyclic compounds to include an intramolecular nitrile oxide cycloaddition (INOC)[14] as the key step. We began our efforts by preparing *N*-homoallyl substituted triazole **18** from oxadiazole **17**.[9] Compound **19,** containing a formyl group at the 5-position of the triazole, was synthesized in good yield (76%) via lithiation of **18** followed by treatment with DMF. However, attempts at formylating **18-a**, which contains an *N*–homopropargyl group, under the same conditions resulted primarily in decomposition to an *N*-unsubstituted triazole **5** ($R^1 = H$) and a low yield of **19-a**. Subsequent formation of aldoximes **20** and **20-a** from corresponding **19** and **19-a**, followed by intramolecular nitrile oxide cycloaddition of in situ formed **21** and **21-a**, afforded the annulated heterocycles **22** and **22-a**, respectively. The structure of the annulated compound **22** was confirmed via X-ray crystallography (Fig. 3).[17]

In conclusion, routes for the regiospecific synthesis of 3-(triazol-3-yl)-1,2-isoxazol(in)e-5-yl-aryl derivatives (**15**, **16**)[15] and novel annulated compounds (**22**, **22-a**)[16] have been developed, employing intermolecular and intramolecular nitrile oxide 1,3-dipolar cycloadditions, respectively. Exploiting this methodology, the construction of compound libraries as well as the evaluation of biological activities are underway.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.06.034. These data include MOL files and InChiKeys of the most important compounds described in this article.

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15. *General procedure for the Synthesis of 3-(traizol-3-yl)-1,2-isoxazol-5-yl-aryl derivatives **15** or **16**:* To the solution of aldoxime (**12**, 0.648 mmol) and dipolarophile (10 equiv) in THF (8 mL) was added bleach (NaOCl; 6.15%, 2.5 equiv) slowly for 20 min at rt. The reaction mixture was stirred at rt for 2 h, then the resultant mixture was treated with ethyl acetate and water. The organic layer was separated, dried ($MgSO_4$), and purified by column chromatography using hexane and ethyl acetate as an eluent to provide pure product **15** or **16**.
16. *Procedure for the Synthesis of 3-phenyl-5,6,6a,7-tetrahydro[1,2]oxazolo[3,4-c][1,2,4]triazolo[4,3-a][yridine (**22**):* To the solution of aldoxime (**20**, 0.3 g, 1.24 mmol) in THF (10 mL) was added bleach (NaOCl; 6.15%, 2.5 equiv)

dropwise via a syringe at room temperature. The reaction mixture was stirred at rt for 2 h, then the resultant mixture was treated with ethyl acetate and water. The organic layer was extracted with ethyl acetate (3 × 30 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The resultant solid was stirred with small amount of ethyl acetate (10 mL), then filtered to provide pure product **22** as a solid (0.14 g, 47% yield). mp: 253–254 °C (decom), LC/MS: *m*/*z* 241.1 (M^++1), ^{1}H NMR (500 MHz, CD_2Cl_2): δ 7.78–7.76 (m, 2H), 7.60–7.58 (m, 3H), 4.90 (m, 1H), 4.38–4.30 (m, 2H), 3.90–3.84 (m, 2H), 2.57–2.52 (m, 1H), 2.08–1.99 (m, 1H). ^{13}C NMR (125 MHz, CD_2Cl_2): δ 156.02, 149.59, 145.81, 131.93, 130.23, 129.80, 127.29, 75.48, 46.41, 45.72, 27.87.

17. Crystallographic data for the structures in this paper have been deposited at the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC #1430300 and 1430301. Copies of these data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(1223)336033 or e-mail: deposit@ccdc.cam.ac.uk or via www.ccdc.cam.ac.uk/conts/retrieving.html.