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# L-Proline catalyzed one-step synthesis of 4,5-diaryl-2*H*-1,2,3-triazoles from heteroaryl cyanostilbenes via [3+2] cycloaddition of azide

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## Abstract

Use of a novel reagent has been established for the synthesis of a series of 4,5-diaryl-2*H*-1,2,3-triazoles (**6a-i** and **9a-e**) from cyanostilbene analogs of benzo[*b*]thiophene, benzo[*b*]furan and indole, catalyzed by L-proline via Lewis base-catalyzed one-step [3+2]cycloaddition of azide. This method provides an efficient, simple and environmentally benign procedure that affords good yields and relatively short reaction times.

### Keywords

4,5-Diaryl-2*H*-1,2,3-triazoles; L-Proline; Heteroaryl cyanostilbenes; Sodium azide; [3+2] Cycloaddition of azide

Recent studies on cyanostilbene anticancer agents (Fig 1. **1**-**3a**) have focused on the construction of bridge units between the two aromatic ring systems to overcome the instability of the molecules due to *cis*, *trans*-isomerization in solution.[1-5] Diverse biological activities have been documented for drug molecules that incorporate the triazole ring system, including anti-cancer,[6-8] anti-bacterial,[9] anti-fungal[10] and anti-convulsant activities.[11] Recently, we reported the synthesis of a variety of heterocyclic cyanstilbene analogs as anti-cancer agents.[12] In the view of the promising biological activity of the triazole analogs and in continuation of our research work on cyanostilbene analogs (Fig 1; **2** and **3a**)[12] as novel anticancer agents, we focused on the incorporation of a triazole bridge unit between the two aromatic ring systems of such molecules by chemical modification of cyanostilbene moiety (Scheme 1). Unlike compounds **1-3a**, the resulting 4,5-



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disubstituted-2*H*-1,2,3-triazole analogs cannot undergo *cis-trans* isomerization, providing molecules with greater stability (e.g. Scheme 1; **6a**).

The formation of 4,5-disubstitued-1*H*- and 2*H*-1,2,3-triazoles ring system is well known in the literature as “click chemistry” reaction products from Cu-catalyzed azide-alkyne 1,3-dipolar cycloaddition (CuAAC) reactions.[13-14] Although the thermal reaction between alkyne and $NaN_3$ “click chemistry” synthesis of 4,5-disubstitued-2*H*-1,2,3-triazoles is well known, the low yields, difficulty in preparation of substituted alkynes and cost effectiveness are limitations of this reaction.[15] Zard et al.[16] reported the synthesis of 1,2,3-(2*H*)-triazoles by the reaction of α-substituted nitroalkenes with excess of $NaN_3$ at 80-90 °C in 54-96% yield. In this reaction the yield of the products depends on the substrate but the preparation of the olefin precursor became challenge. Synthesis of 4,5-disubstituted-2*H*-1,2,3-triazoles was also reported by cycloaddition of internal alkynes with alkyl azides or metal azides, this procedure has limitations such as low yields, if the alkyne reactant is conjugated with an aryl group containing electron donating substituents.[17] Another approach for the synthesis of 4,5-disubstitued-2*H*-1,2,3-triazoles from nitroalkenes was reported utilizing $NaN_3$ and L-proline to afford product yields in the range 40-89%.[18] However, for this reaction the vinyl group is essential, and the reaction has to be carried out at room temperature, necessitating elongated reaction times, since facile polymerization of the nitroalkene reactant occurs at elevated temperatures. Very recently, we reported the synthesis of 4,5-substituted 2*H*-1,2,3-triazoles from (*Z*)-2,3-diphenyl substituted acrylonitriles using excess $NaN_3$ (3 equivs) and $NH_4Cl$ in DMF at reflux temperatures for 12 h in 59-87% yields.[19]

In the present communication we describe the synthesis of 4,5-diaryl-2*H*-1,2,3-triazoles from heteroaryl cyanostilbenes utilizing L-proline as a Lewis base and $NaN_3$ in dimethyl sulfoxide at 100 °C. Under these conditions, the reaction time is 1-6 h, and yields are in the range 75-96%.

In an earlier communication we reported the one-step synthesis of heteroaryl cyanostilbene analogs by the reaction of benzthiophene-2-aldehyde with phenyl acetonitriles in 5% sodium methoxide/methanol solution for 3 h (Scheme 1).[12] This reaction predominantly forms the *trans*-isomer (**3a**) which slowly converts to the respective *cis*-isomer (**2**) in organic solvents; more rapid *trans to cis* conversion takes place in the presence of protic solvents and on exposure to light. To avoid this geometrical isomerism we sought to lock the geometry of cyanostilbenes (**3a-i**) by converting them to their corresponding 1,2,3-(2*H*)-triazole analogs (**6a-i**) by reaction with $NaN_3$/DMSO in the presence of a Lewis base such as L-proline (Scheme 2). The initial reaction conditions utilized for the synthesis of the representative compound **6a** from cyanostilbene **3a**, are summarized in Table 1. The formation of the 4,5-disubstitued-2*H*-1,2,3-triazole **6a** was confirmed by single crystal X-ray diffraction analysis (Figure 2), and from subsequent regiospecific *N*-2 methylation with methyl iodide/$K_2CO_3$ in acetone to form **7** (Scheme 1; Figure 2).

Heating (*Z*)-3-(benzo[*b*]thiophen-2-yl)-2-(3,4,5-trimethoxy phenyl)acrylonitrile (**3a**) with $NaN_3$ (2 equivs) in DMSO under reflux for 36 h in the absence of Lewis base afforded poor yields (15%) of **6a**. The yield of **6a** was significantly improved when the reaction was carried out using excess $NaN_3$ (3 equivs) in the presence of $NH_4Cl$ in DMSO at 120 °C for

18 h (51%). In attempts to further improve yield and reduce reaction time, different base catalysts were utilized (i.e. L-proline, TMSA, TEA, pyrrolidine, and KOt-But). L-proline (96%) was found to be the most suitable catalyst for this reaction, with the additional advantages of being efficient, and environmentally benign.

A variety of different heteroaryl *trans*-cyanostilbene analogs (**3a-i** and **8a-e**) containing variously substituted phenyl ring systems were used to study the scope of the reaction (Scheme 2 and 3), and the effect of structure on reaction rate and yield; the results obtained are provided in Tables 2 and 3. This reaction was also carried out using a *cis*-cyanostilbene analog as starting material, i.e. (*E*)-3-(benzo[*b*]thiophen-2-yl)-2-(3,4,5-trimethoxy phenyl)acrylonitrile (**2**) as a model reactant, to compare the rate of reaction and yield of **6a** in comparison with its corresponding *Z*-isomer (**3a**). The rate of reaction using *E*-isomer **2** was about half the rate of the reaction using the *Z*-isomer **3a**, and the yield of **6a** from **2** was only 78%. Overall yields for the 2- and 3-benzo[*b*]thiophenyl-, 2- and 3-indolyl- and 2-benzo[*b*]furanyl-2*H*-1,2,3-triazole products were in the range 96-75%.

A plausible mechanism for the above reaction is provided in Scheme 4. Initial Michael addition of azide ($N_3^-$) ion generates carbanion **10** followed by internal cyclization to form the triazole species **11**. Loss of the cyano group then yields **12**, followed by Lewis base-catalyzed prototropy to afford the 2*H*-1,2,3-triazole product **6a**.

In conclusion, a novel one-step synthesis of a series of benzothiophenyl, benzofuranyl, and indolyl, 2*H*-1,2,3-triazoles from corresponding *trans*-cyanostilbene precursors has been developed. This method involves use of a novel reagent, L-proline, a Lewis base-catalyzed [3+2]cycloaddition of azide across the cyanostilbene double bond. The procedure affords good yields and short reaction times, and provides an efficient, simple and eco-friendly procedure for the synthesis of a variety of 4,5-diaryl-2*H*-1,2,3-triazoles.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

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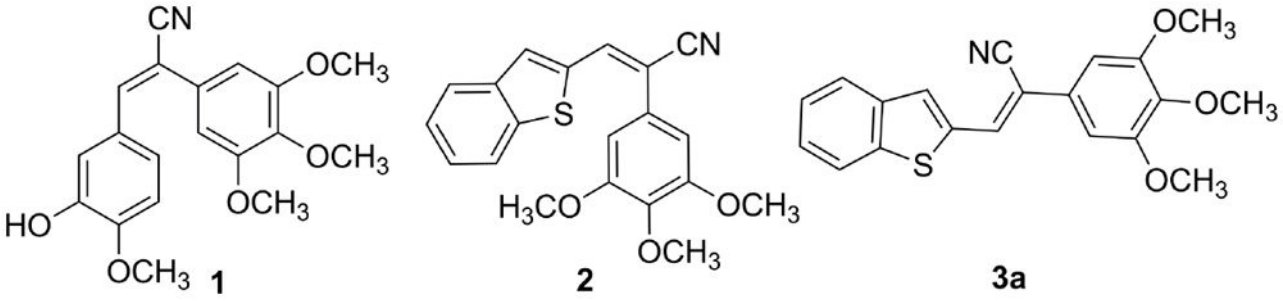



**Figure 1.**
Cyanostilbene analogs

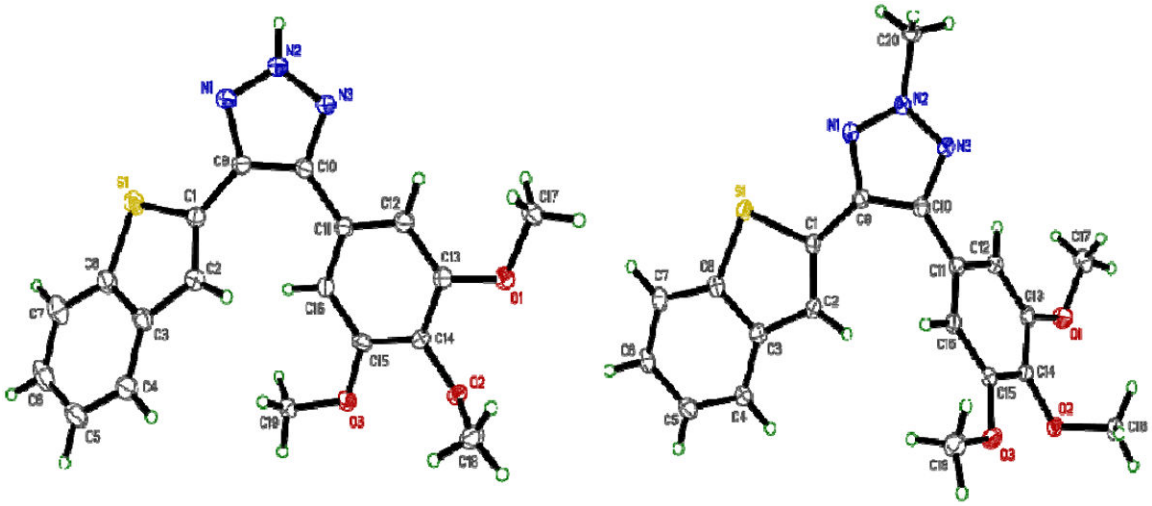
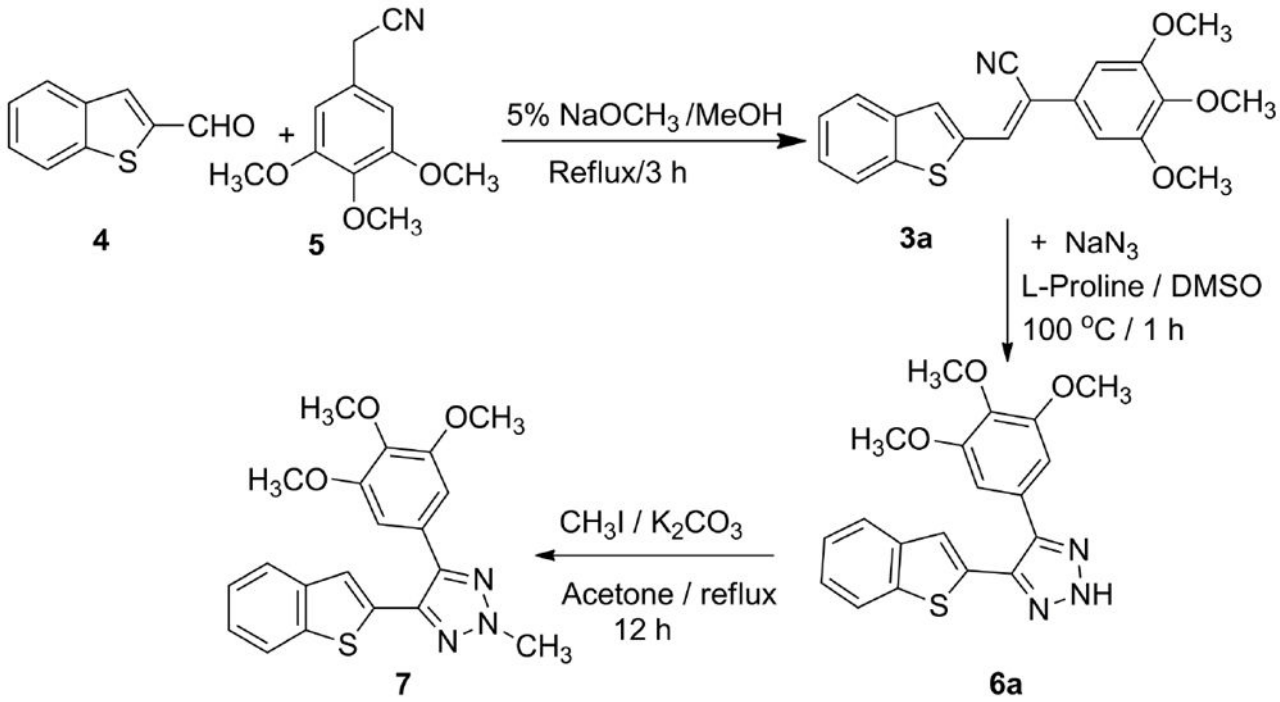


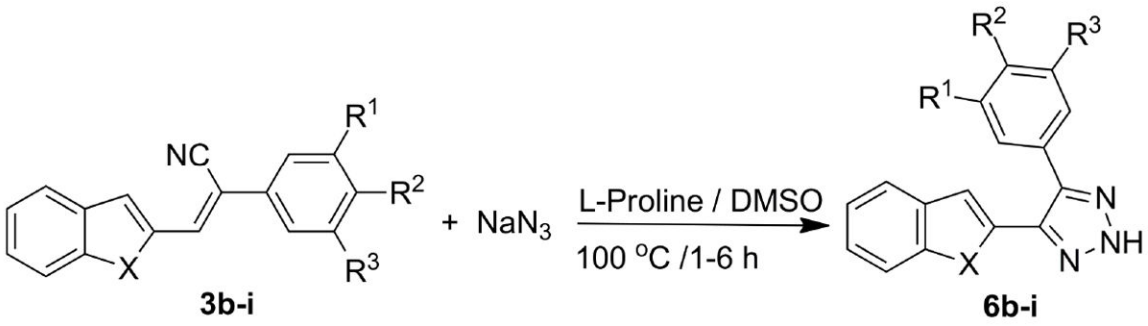

**Figure 2.**

Single crystal X-ray structures of 4-(benzo[*b*]thiophen-2-yl)-5-(3,4,5-trimethoxyphenyl)-2*H*-1,2,3-triazole (**6a**) and 4-(benzo [*b*] thiophen-2-yl)-2-methyl-5-(3,4,5-trimethoxyphenyl)-2*H*-1,2,3-(2*H*)-triazole (**7**).



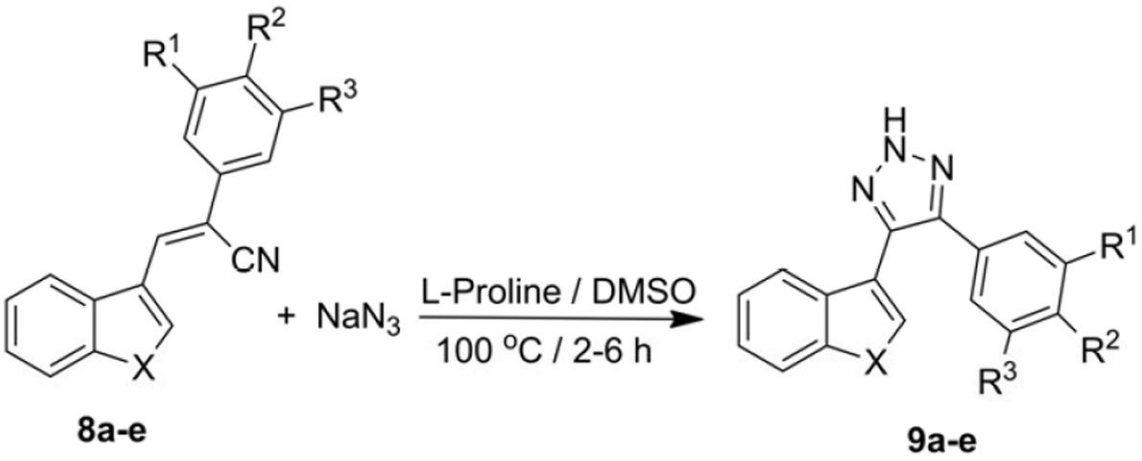

**Scheme 1.**

Synthesis of 4-(benzo[*b*]thiophen-2-yl)-5-(3,4,5-tri methoxyphenyl)-2*H*-1,2,3-triazole (**6a**) and 4-(benzo[b] thiophen-2-yl)-2-methyl-5-(3,4,5-trimethoxyphenyl)-1,2,3-(2*H*)-triazole (**7**).

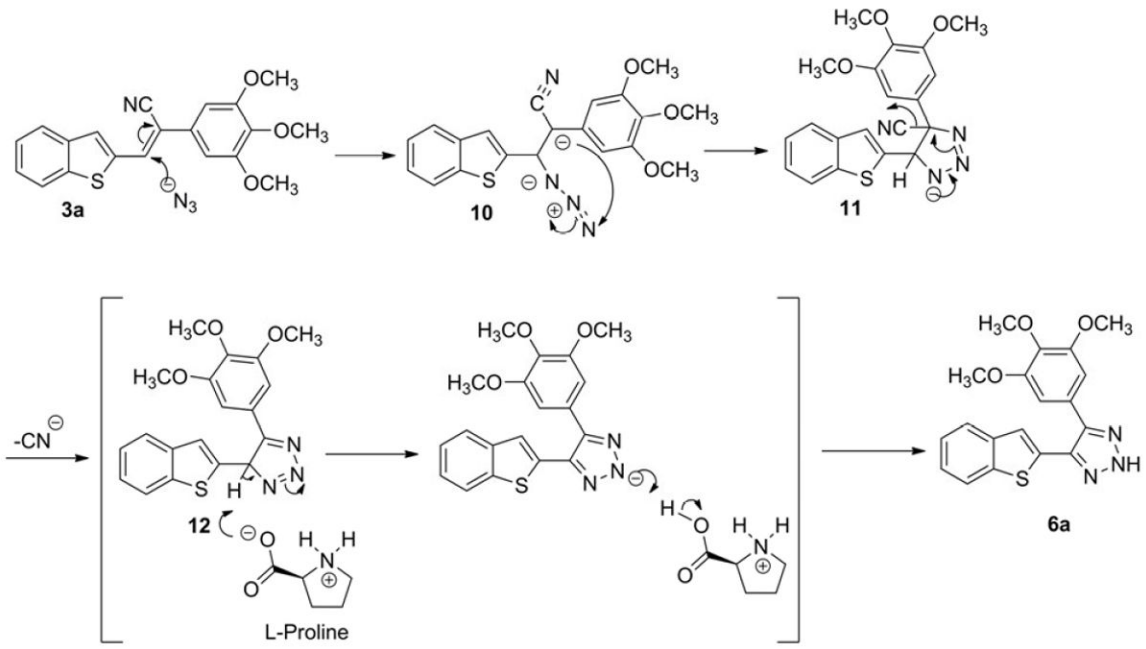



**Scheme 2.**

Synthesis of substituted 4-heteroaryl-5-phenyl-2*H*-1,2,3-triazoles (**6b-i**)




**Scheme 3.**
Synthesis of substituted 4-(benzo[*b*]thiophen-3-yl)-5-phenyl-2*H*-1,2,3-triazoles (**9a-e**).




**Scheme 4.**

Plausible mechanism for the formation of 4-(benzo [*b*]thiophen-2-yl)-5-(3,4,5-trimethoxyphenyl)-2*H*-1,2,3-triazole (**6a**) from **3a** via 3+2 cycloaddition of azide.

**Table 1**

Different reaction conditions for the formation of **6a** from **3a** via 3+2 cycloaddition of azide.

| Catalyst | Solvent | $NaN_3$ Equiv. | Temp (°C) | Time (h) | Yield[c] (%) |
|---|---|---|---|---|---|
| $NH_4Cl$ (2.0) | DMSO | 2 | 120 | 18 | 45 |
| $NH_4Cl$ (2.0) | DMSO | 3 | 120 | 18 | 51 |
| $NH_4Cl$ (2.0) | DMF | 2 | 120 | 20 | 40 |
| - | DMSO | 2 | 120 | 36 | 15 |
| TMSA[a](1.1) | DMSO | 2 | 120 | 20 | 65 |
| TMSA (1.1) | DMF | 2 | 120 | 24 | 62 |
| L-pro | DMSO | 1 | rt | 20 | 75 |
| L-pro | DMSO | 1 | 100 | 1 | 96 |
| L-pro | DMSO | 1 | 130 | 1 | 89 |
| L-pro | Acetonitrile | 2 | 82 | 5 | 0 |
| TEA (1.2)[b] | DMSO | 1 | 100 | 10 | 18 |
| Pyrrolidine (1.2) | DMSO | 1 | 100 | 6 | 33 |
| KOt-Bu (1.2) | DMSO | 1 | 100 | 12 | 15 |

[a]TMSA: trimethyl silyl azide,

[b]TEA: Triethyl amine,

[c]isolated yields.

**Table 2**

Effect of different heteroaryl-2-yl cyanostilbenes in the synthesis of a variety of 2*H*-1,2,3-triazoles (**6a-i**).

| Entry | X | $R^1$ | $R^2$ | $R^3$ | Time | Yield[a] |
|---|---|---|---|---|---|---|
| | | | | | (h) | (%) |
| **6a** | S | $OCH_3$ | $OCH_3$ | $OCH_3$ | 1 | 96 |
| **6b** | S | $OCH_3$ | H | $OCH_3$ | 3 | 94 |
| **6c** | S | H | $OCH_3$ | H | 4 | 90 |
| **6d** | S | OH | $OCH_3$ | H | 6 | 75 |
| **6e** | S | 3,4-methylene dioxy | | H | 5 | 86 |
| **6f** | S | H | $SCH_3$ | H | 5 | 84 |
| **6g** | O | $OCH_3$ | $OCH_3$ | $OCH_3$ | 3 | 93 |
| **6h** | O | $OCH_3$ | H | $OCH_3$ | 4 | 91 |
| **6i** | NH | $OCH_3$ | $OCH_3$ | $OCH_3$ | 4 | 91 |

[a] isolated yields.

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**Table 3**

Effect of different heteroaryl-3-yl cyanostilbenes in the synthesis of 2*H*-1,2,3-triazoles (**9a-e**).

| Entry | X | $R^1$ | $R^2$ | $R^3$ | Time | Yield[a] |
|---|---|---|---|---|---|---|
| | | | | | (h) | (%) |
| **9a** | S | $OCH_3$ | $OCH_3$ | $OCH_3$ | 2 | 92 |
| **9b** | S | $OCH_3$ | $OCH_3$ | H | 6 | 88 |
| **9c** | S | H | $OCH_3$ | H | 5 | 84 |
| **9d** | NH | $OCH_3$ | $OCH_3$ | $OCH_3$ | 4 | 91 |
| **9e** | NH | $OCH_3$ | H | $OCH_3$ | 5 | 89 |

[a] isolated yields.