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First regioselective iodocyclization reaction of 3-aryl-5-(prop-2-ynylthio)-1*H*-1,2,4-triazoles

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ABSTRACT

The regioselective iodocyclization reaction of 3-aryl-5-(prop-2-ynylthio)-1*H*-1,2,4-triazoles is described for the first time. The iodocyclization reaction of 3-aryl-5-(prop-2-ynylthio)-1*H*-1,2,4-triazoles using molecular iodine afforded diiodo-compound which on CuI-catalyzed intramolecular C–N coupling reaction gave six-membered 2-aryl-5*H*-[1,2,4]triazolo[5,1-*b*][1,3]thiazines, whereas, the five membered 3-aryl-5,6-dihydrothiazolo[2,3-*c*][1,2,4]triazoles were obtained exclusively when the iodocyclization reaction of 3-aryl-5-(prop-2-ynylthio)-1*H*-1,2,4-triazoles was carried out using NIS.

In recent decades, the chemistry of 1,2,4-triazoles and their fused heterocyclic derivatives has received considerable attention due to their interesting biological activities.[1] However, systems containing both nitrogen and sulfur atoms in the same heterocycles showed remarkable properties and have proved to be suitable for the development of functional organic materials as well as pharmaceutically important molecules.[2] In view of this, the thiazolo[3,2-*b*]-[1,2,4]triazole core is found in biologically active compounds possessing antimicrobial,[3] antibacterial,[4] G-quadruplex stabilizing,[5] and anti-inflammatory[6] activities whereas, thiazine compounds are found to show a number of biological activities such as anticancer,[7] antileukemic,[8] antibacterial,[9] and antihypertensive[10] activities. In contrast, few articles devoted to the synthesis of 2-aryl-5*H*-[1,2,4]triazolo[5,1-*b*][1,3]thiazine[11] as compared to 3-aryl-5,6-dihydrothiazolo[2,3-*c*][1,2,4]triazole have been published.[12]

Recently, electrophilic cyclization of an unsaturated C–C bond with a wide variety of nucleophiles, including C, N, O, S, and Se nucleophiles has emerged as versatile tool for the synthesis of various heterocycles.[13] Reports are available in the literature for the synthesis of heterocycles via iodocyclization reaction of alkynes containing heteroatom using *N*-nucleophiles for example, iodocyclization reaction of 2-anilino-3-(prop-2-ynyl)-l-imidazolinone,[14] alkynyl-sulfonamides,[15] *N*-protected *o*-(alkynyl)anilines,[16] *N*,*N*-dialkyl-2-(1-alkynyl)anilines,[17] 2-alkynylbenzaldoximes,[18] 2-alkynyl benzyl azides,[19] or (pyridinyl)propynyl acetates.[20] To the best of our knowledge, no reports can be found in the literature for the iodocyclization reaction in which 1,2,4-triazolyl nitrogen acts as an internal nucleophile on alkynyl-carbon for the synthesis of fused heterocyclic derivatives. Very recently, we reported the synthesis of bicyclic-β-lactams via the regioselective iodocyclization reaction of allene-thioureas.[21] In continuation with our ongoing project based on the development of efficient methodologies to explore the new type of heterocyclic compounds which might have potential biological activities, herein for the first time, in this Letter we describe the regioselective iodocyclization reaction of 3-aryl-5-(prop-2-ynylthio)-1*H*-1,2,4-triazoles for the synthesis of 2-aryl-5*H*-[1,2,4]triazolo[5,1-*b*][1,3]thiazines and 3-aryl-5,6-dihydrothiazolo[2,3-*c*][1,2,4]triazoles.

Our synthetic approach begun with triazolethiones **1**, which were readily prepared from aromatic carboxylic acids by the previously known procedure in three steps.[22] Further, the selective monoalkylation of triazolethiones **1** with propargyl bromide under neutral condition resulted in the formation of 3-aryl-5-(prop-2-ynylthio)-1*H*-1,2,4-triazoles **2** in good yields (Table 1, entries 1–9). The structure of the 3-aryl-5-(prop-2-ynylthio)-1*H*-1,2,4-triazoles **2** was confirmed by the studies of spectral analysis.[23]

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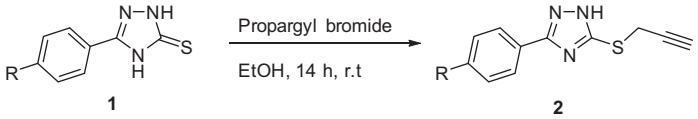
Table 1
Synthesis of 3-aryl-5-(prop-2-ynylthio)-1*H*-1,2,4-triazoles **2**[a]

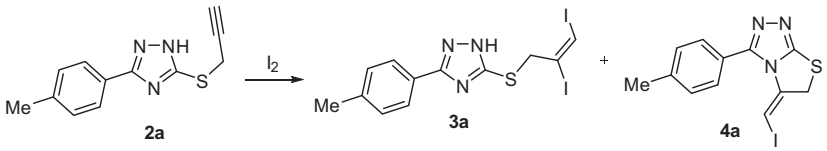


1 **2**

Entry	R	Product	Yield[b] (%)
1	Me	**2a**	69
2	H	**2b**	74
3	CF_3	**2c**	62
4	OH	**2d**	69
5	OMe	**2e**	70
6	NH_2	**2f**	77
7	F	**2g**	68
8	Cl	**2h**	72
9	NO_2	**2i**	69

[a] The reaction was carried out as follows, 1.0 equiv of triazolethiones (**1**), 1.0 equiv of propargyl bromide in ethanol at 25 °C.
[b] Isolated yields.

Table 2
Optimization conditions for the iodocyclization reaction of 3-aryl-5-(prop-2-ynylthio)-1*H*-1,2,4-triazoles **2**[a]



2a **3a** **4a**

Entry	I_2 (equiv)	Base	Solvent	Time (h)	Yield[b] (%)	
					3a	**4a**
1	1.5	–	DCM	18	79	Traces
2	2.0	–	DCM	12	92	Traces
3	2.5	–	DCM	10	81	Traces
4	2.0	–	Methanol	48	37	22
5	2.0	–	THF	36	74	9
6	2.0	–	Toluene	36	69	7
7	2.0	–	DMF	48	25	15
8	2.0	–	$CHCl_3$	12	87	7
9	2.0	K_2CO_3	THF	3	29	9
10	2.0	K_2CO_3	DCM	6	60	16
11	2.0	K_2CO_3	DMF	3	Traces	40

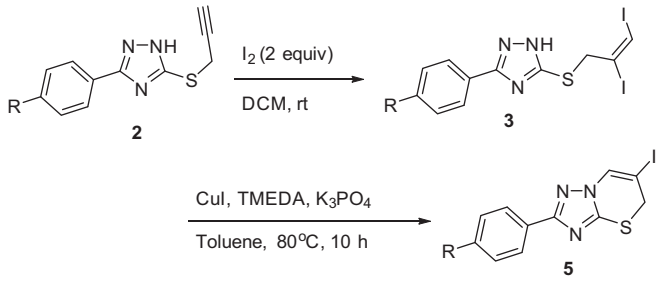
[a] Iodocyclization reactions were conducted using 0.437 mmol of **2a** at rt.
[b] Isolated yields.

The key starting materials **2** in hand, we turned out attention toward the iodocyclization reaction. Firstly, the iodocyclization reaction of compound **2a** was carried out using 1.5 equiv of iodine in DCM at room temperature (Table 2, entry 1). The reaction took place readily and the diiodo-compound **3a** was formed in 79% yield with traces of five-membered compound **4a** (entry 1). As shown in Table 2, different reaction conditions were screened to improve the yield of diiodo-compound **3a**. Best result was obtained when the reaction was carried out using 2 equiv of iodine in DCM to afford diiodo-compound compound **3a** in 92% yield along with traces of five-membered compound 3-(*p*-tolyl)-5,6-dihydrothiazolo[2,3-*c*][1,2,4]triazole **4a** (entry 2).[24] When the polar solvents were used in the reaction, the diiodo-compound **3a** was formed in low yields along with five-membered compound **4a** (entries 4–5 and 8–9). In methanol the compound **4a** was formed in 22% yield (entry 5). Further, to improve the yield of five-membered 3-(*p*-tolyl)-5,6-dihydrothiazolo[2,3-*c*][1,2,4]-triazole **4a** the iodocyclization reactions was carried out under basic condition using K_2CO_3 as a base (entries 9–11). The yield of the product 3-(*p*-tolyl)-5,6-dihydrothiazolo[2,3-*c*][1,2,4]triazole **4a** was improved to 40% when the reaction was carried out in DMF using K_2CO_3 as a base (entry 11).

Next, we focused our attention toward the synthesis of diiodo-compound **3** (Table 3). The reaction of various 3-aryl-5-(prop-2-ynylthio)-1*H*-1,2,4-triazoles **2** was carried out under optimal conditions (Table 3). The diiodo-compound 2-aryl-5*H*-[1,2,4]triazolo[5,1-*b*][1,3]thiazines **3** were formed in good to excellent yields (Table 3, entries 1–9). A variety of functional groups such as electron donating as well as electron withdrawing groups were well tolerated under the present reaction conditions (entries 1–9). The structure of compounds **3** was confirmed by the studies of IR, ^{1}H NMR, ^{13}C NMR, NOESY, and HRMS spectral analysis.[24] Finally, the structure of the diiodo-compound **3h** was confirmed by X-ray crystallography (see Supporting information).

In recent years, the copper-mediated Ullmann-type intramolecular C–N coupling reactions have developed as an important approach to heterocyclic compounds.[25] The intramolecular C–N coupling reaction of diiodo-compound **3a** using 20 mol % of CuI,

Table 3
Synthesis of 2-aryl-5*H*-[1,2,4]triazolo[5,1-*b*][1,3]thiazines **5a**–**i**[a]



Entry	R	Time (h)	% yield[b,c] (**3**)	% yield[b,d] (**5**)
1	Me	12	92 (**3a**)	72 (**5a**)
2	H	12	81 (**3b**)	67 (**5b**)
3	CF_3	12	83 (**3c**)	58 (**5c**)
4	OH	12	81 (**3d**)	– (**5d**)[e]
5	OMe	12	89 (**3e**)	62 (**5e**)
6	NH_2	13	75 (**3f**)	– (**5f**)[e]
7	F	12	77 (**3g**)	65 (**5g**)
8	Cl	11	82 (**3h**)	63 (**5h**)
9	NO_2	13	83 (**3i**)	48 (**5i**)

[a] Reaction was carried out using 0.437 mmol of **2** and 2 equiv of iodine in DCM at rt.
[b] Isolated yields.
[c] Five-membered 3-aryl-5,6-dihydrothiazolo[2,3-*c*][1,2,4]triazoles **4** were formed in traces.
[d] Reaction was carried out using 0.20 mmol of **3**, 20 mol % of CuI, 40 mol % of TMEDA, and 2 equiv of K_3PO_4 in Toluene at 80 °C for 10 h.
[e] Reaction not resulted in the formation of required product whereas, longer reaction time resulted in the decomposition of starting material.

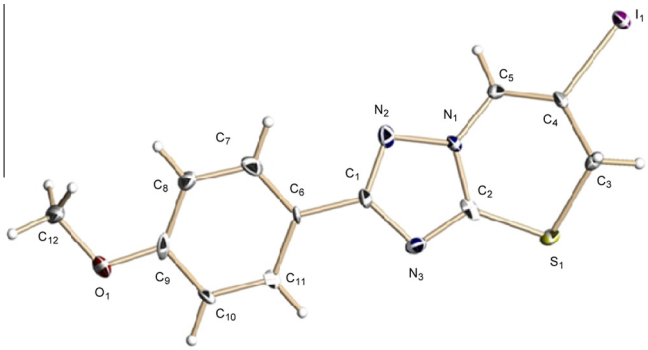
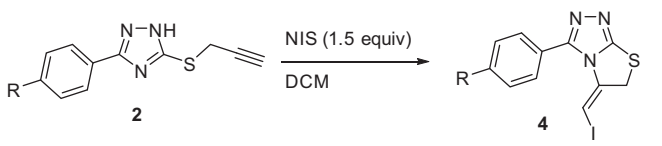


Figure 1. The X-ray crystallographic structure of **5e**.

40 mol % of TMEDA, and 2 equiv of K_2CO_3 in toluene at 80 °C readily afforded the six-membered 2-aryl-5*H*-[1,2,4]triazolo[5,1-*b*][1,3]thiazine **5a** in 35% yield (see Supporting information). To improve the yield of coupling reaction, different conditions were then screened. We found that the reaction was highly dependent on the type of base used[26] and the best result was obtained when the reaction was carried out using 2.0 equiv of K_3PO_4 (Table 3, entry 1, 72% yield).[27] Inspired by this result, the intramolecular C–N coupling reaction of other diiodo-compounds **3** was carried out under above conditions (Table 3, entries 1–9). The variety of functional groups such as –Me, $–CF_3$, –OMe, –F, Cl, and $–NO_2$ at the aromatic ring was well tolerated under the reaction conditions and afforded the desired six-membered 2-aryl-5*H*-[1,2,4]triazolo[5,1-*b*][1,3]thiazines **5** in good to moderate yields (entries 1–3, 4, and 7–9). The intramolecular C–N coupling reactions failed when –OH and $–NH_2$ groups were at aromatic ring (entries 4 and 6). The structure of compounds **5** was confirmed by the studies of IR, ^{1}H NMR, ^{13}C NMR, NOESY, and HRMS spectral analysis.[28]

Table 4
Synthesis of 3-aryl-5,6-dihydrothiazolo[2,3-*c*][1,2,4]triazoles via iodocyclization reaction of **2**[a]



Entry	R	Time (min)	Product	Yield[b] (%)
1	Me	20	**4a**	55
2	H	20	**4b**	48
3	CF_3	20	**4c**	58
4	OMe	20	**4d**	59
5	F	20	**4e**	49
6	Cl	20	**4f**	51
7	NO_2	20	**4g**	44
8	NH_2	2 h	**4h**	Traces

[a] The reaction was carried using out using 0.437 mmol of **2** and 1.5 equiv of NIS in DCM at rt.
[b] Isolated yields.

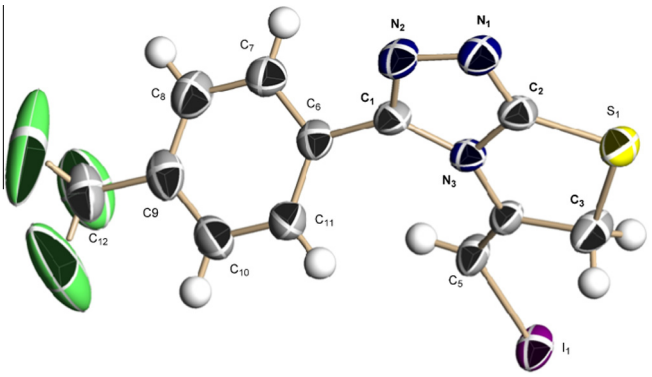


Figure 2. The X-ray crystallographic structure of **4c**.

The present Cu-catalyzed intramolecular C–N coupling reaction is highly regioselective and the regioisomers, five-membered 3-aryl-5,6-dihydro thiazolo[3,2-*b*]-[1,2,4]triazole or six-membered 3-aryl-7*H*-[1,2,4]triazolo[3,4-*b*][1,3]thiazine were never formed under these reaction conditions. Finally, the structure of the representative six-membered compound **5e** was confirmed by X-ray crystallography (Fig. 1).[29]

Encouraged by this finding, we searched for another catalyst which would allow us to access the 3-aryl-5,6-dihydrothiazolo[2,3-*c*][1,2,4]triazoles **4** as major products. Interestingly, when the iodocyclization reaction of compound **2a** was carried out using 1.5 equiv of NIS as catalyst in DCM at room temperature the five-membered compound **4a** was formed exclusively in 55% yield (Table 4, entry 1).[30,31] Under this reaction condition the cyclization of other 3-aryl-5-(prop-2-ynylthio)-1*H*-1,2,4-triazoles **2b**–**h** was carried out to afford **4b**–**h** (entries 2–9). Functional groups such as alkyl, methoxy, halogens, trifluoromethyl, and nitro were well tolerated under the present reaction conditions (entries 1–7). When the electron donating amine compound **2f** was used in the reaction, the required compound **4h** was formed in traces (entry 8). This approach is highly regioselective for five-membered 3-aryl-5,6-dihydrothiazolo[2,3-*c*][1,2,4]triazoles **4**. The compounds **4a**–**h** were formed with *E*-configuration whereas, compounds with *Z*-configuration were not formed under these reaction conditions. The structure of the compounds **4** was confirmed by the studies of IR, ^{1}H NMR, ^{13}C NMR, NOESY, and HRMS spectral analysis. Finally, the molecular structure of the representative compound **4c** was determined by the X-ray crystallography (Fig. 2).[32]

In conclusion, the first regioselective iodocyclization reaction of 3-aryl-5-(prop-2-ynylthio)-1*H*-1,2,4-triazoles is described. The iodocyclization reaction of 3-aryl-5-(prop-2-ynylthio)-1*H*-1,2,4-triazoles using molecular iodine afforded the diiodo-compound which on CuI-catalyzed intramolecular C–N coupling reaction gave six-membered 2-aryl-5*H*-[1,2,4]triazolo[5,1-*b*][1,3]thiazines whereas, the use of NIS in the reaction afforded the five membered 3-aryl-5,6-dihydrothiazolo[2,3-*c*][1,2,4]triazoles. The present approach provides access to a substituted fused heterocycles. Further investigation on the application of this reaction is in progress.

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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.2015.07.006.

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23. *General procedure for the propargylation reaction of* **1**: To a solution of triazolethiones (5.23 mmol) in ethanol (10 mL), propargyl bromide (0.396 mL, 5.23 mmol) was added and allowed to stir for 12 h at rt. The reaction mixture was concentrated and the residue was extracted with ethyl acetate and organic phase washed was with brine, dried over Na_2SO_4, filtered and evaporated in vacuo. The residue was purified by column chromatography on silica gel using ethyl acetate:pet ether (1.5:8.5) as eluent to give the corresponding products **2a**–**2i**.
24. *General procedure for the iodocyclization reaction of* **3**: To a solution of **2** (100 mg, 0.436 mmol) in CH_2Cl_2 (5 mL) was added I_2 (223 mg, 0.873 mmol) at room temperature. After stirring at this temperature (12 h), the reaction mixture was extracted with CH_2Cl_2 and washed with saturated $Na_2S_2O_3$ and $NaHCO_3$. The organic phase was washed with brine, dried over Na_2SO_4, filtered and evaporated in vacuo. The residue was chromatographed on silica gel using ethyl acetate:pet ether (1:9) as eluent to give corresponding product (**3a**–**3i**).
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27. For optimization conditions see Supporting information.
28. *General procedure for the synthesis of* **5**: A round bottom flask was charged with **3** (0.20 mmol), TMEDA (40 mol %), K_3PO_4 (0.41 mmol), CuI (20 mol %) and toluene (5 mL). The reaction mixture was stirred at 80 °C for 10 h, then aqueous solution of sodium thiosulfate was added and the mixture was extracted with ethyl acetate. The combined organic phase was washed with brine and dried over Na_2SO_4. Purification of the crude mixture by flash chromatography on silica gel using ethyl acetate:pet ether (1:9) as eluent to afford the product **5**.
29. CCDC 1043642 for **5e** contains the supplementary crystallographic data for this Letter. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
30. For optimization conditions see Supporting information.
31. *General procedure for the iodocyclization reaction of* **4**: To a solution of **2** (100 mg, 0.436 mmol) in CH_2Cl_2 (5 mL) was added NIS (147 mg, 0.655 mmol)

at room temperature. After stirring at this temperature (20 min), the reaction mixture was extracted with CH_2Cl_2 and washed with saturated $Na_2S_2O_3$ and $NaHCO_3$. The organic phase was washed with brine, dried over Na_2SO_4, filtered, and evaporated in vacuo. The residue was chromatographed on silica gel using ethyl acetate:pet ether (1:9) as eluent to give corresponding product (**4a**–**4g**).

32. CCDC 1043644 for **4c** contains the supplementary crystallographic data for this Letter. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.