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Silver(I)-Catalyzed Regioselective Synthesis of Triazole Fused-1,5-Benzoxazocinones

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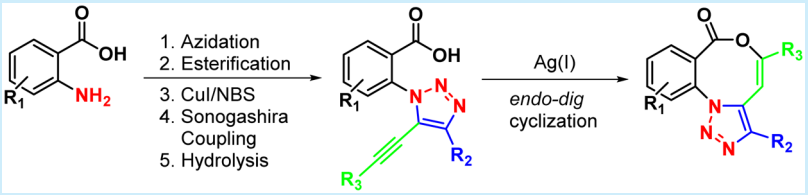
Supporting Information



ABSTRACT: An efficient and regioselective synthesis of novel 1,2,3-triazole-fused-1,5-benzoxazocinones through intramolecular cyclization of substituted ethynyl triazoyl benzoic acids was explored. A crucial precursor 5-iodo-1,2,3-triazole benzoate was obtained from substituted 2-azido benzoic acid esters in a single step through a Copper-Catalyzed Azide−Alkyne Cycloaddition (CuAAC) reaction using a CuI/NBS catalytic system. A carbon−carbon triple bond was installed through a Sonogashira coupling reaction by various terminal alkynes. Finally, the 1,4,5-substituted ethynyl triazoyl benzoic acids were cyclized by a AgOTf-mediated intramolecular cyclization to afford 8-*endo-dig* 1,2,3-triazole-fused-1,5-benzoxazocinones exclusively.

Recently, triazole-fused polycyclic heterocycles have gained much attention owing to their broad spectrum of bioactivities;[1] 1,2,3-triazoles particularly fused with heterocycles at the 1,5-positions such as triazolo 1,5-benzodiazepin-2-one **A** were reported to inhibit serine protease.[2] Triazolo-benzoxazepine **B** exhibits promising anticancer activity against multiple cancer cell lines,[3] whereas [1,2,3]-triazolo[1,5-*a*][1,4]benzodiazepine **C** shows antimicrobial effects as well as potent anticancer activity against the A549 lung adenocarcinoma cancer cell line (Figure 1).[4] In recent years, several synthetic

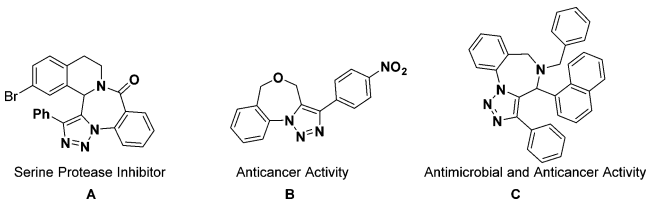


Figure 1. Biologically active 1,2,3-triazole-fused heterocycles.

strategies have been reported for the synthesis of annulated 1,2,3-triazoles at 1,5-positions with other heterocyclic motifs.[5−10] However, a synthetic approach to access 1,2,3-triazole-fused benzoxazocinones is less explored.[1b,3] Therefore, the development of a new and efficient synthetic method is greatly needed to construct novel triazole-fused heterocycles. The biological significance of fused 1,2,3-triazoles prompted us to develop a simple protocol comprising minimum steps for the preparation of 1,2,3-triazole fused benzoxazocinones.

The regular CuAAC reactions are limited to the synthesis of only 1,4-disubstituted 1,2,3-triazoles. In this regard, 5-iodo-1,-2,3-triazole is a useful synthetic precursor since its iodine atom can undergo further transformation into various functional groups to give corresponding trisubstituted triazoles, thereby diversification and functionalization of the 1,2,3-triazole pharmacophore can be achieved.[11]

Intramolecular addition reaction of carboxylic acids to proximate carbon−carbon triple bonds offers an efficient route to the construction of oxygen-containing functionalized heterocycles (Figure 2).[12] According to Baldwin's rules, both *exo-dig* and *endo-dig* cyclizations are possible. Hence, much attention has been focused toward the selective cyclization of an enyne carboxylic acid system.[13] We herein report a

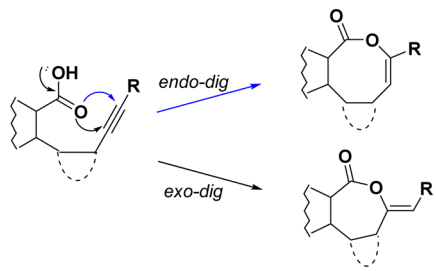


Figure 2. *Endo-dig* and *exo-dig* cyclization mode of enyne carboxylic acid system.

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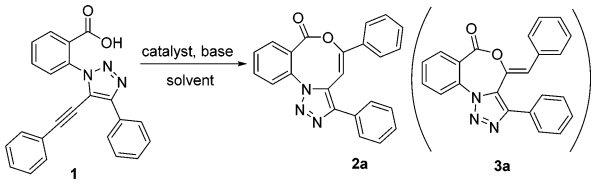
Table 1. Optimization of the Reaction Conditions for Intramolecular Cyclization of Acid 1[a]



entry	catalyst (mol %)	base	additive	solvent	temp (°C)	time (h)	product	yield (%)[b]
1	PTSA (10)	–	–	$CHCl_3$	reflux	16	N.R.	0
2	pyridine	–	–	–	100	16	N.R.	0
3	DBU (10)	–	–	$CHCl_3$	reflux	16	N.R.	0
4	DBU (100)	–	–	$CHCl_3$	100	0.34	**2a**	trace[c]
5	AgOTf (10)	–	–	$CHCl_3$	reflux	16	**2a**	10
6	AgOTf (20)	–	–	$CHCl_3$	reflux	16	**2a**	30
7	AgOTf (50)	K_2CO_3	–	$CHCl_3$	reflux	16	**2a**	50
8	AgOTf (100)	K_2CO_3	–	$CHCl_3$	100	0.34	**2a**	85[c]
9	AgOTf (10)	NaOH	–	$CHCl_3$	100	0.34	**2a**	32
10	$AgSbF_6$ (10)	–	–	$CHCl_3$	reflux	16	N.R.	0
11	AuCl (10)	K_2CO_3	–	CH_3CN	reflux	16	N.R.	0
12	$AuCl_3$ (10)	K_2CO_3	–	CH_3CN	reflux	16	N.R.	0
13	AgOTf (10)	K_2CO_3	PPh_3	$CHCl_3$	100	0.34	**2a**	48
14	AuCl/AgOTf (5)	–	PPh_3	$CHCl_3$	100	0.34	**2a**	trace
15	Ag_2CO_3 (20)	–	–	$CHCl_3$	100	0.34	**2a**	20
16	AgOTf (10)	K_2CO_3	–	toluene	130	0.25	**2a**	87[c]

[a]Reaction conditions: **1** (0.27 mmol), AgOTf (10 mol %), K_2CO_3 (2 equiv), solvent (2 mL). N.R. = No Reaction. [b]Isolated yield. [c]Microwave irradiation.

regioselective synthesis of novel 1,2,3-triazole benzoxazocinones from substituted anthranilic acids. The key step of this strategy includes preparation of a crucial intermediate 5-iodo-1,2,3-triazole benzoate by the CuI/NBS catalytic system and regioselective intramolecular cyclization under the influence of Lewis acid (AgOTf), respectively.

The required precursor acids **1** were prepared by modification of the reported procedure (see Supporting Information). With the key intermediate acid **1** in hand, we next studied the intramolecular cyclization using a variety of catalysts, and the results are summarized in Table 1. Our attempted cyclization of acid **1** under the influence of PTSA, pyridine, or DBU was unsuccessful, and only starting material **1** was recovered (Table 1, entries 1–4). When acid **1** was subjected for cyclization in the presence of 10 mol % of AgOTf in refluxing chloroform for 16 h, a pale yellow solid was obtained in 10% yield with the recovery of acid **1** (Table 1, entry 5). The structure of the isolated solid was identified as (*Z*)-3,5-diphenyl-7*H*-benzo[*c*][1,2,3]triazolo[1,5-*e*][1,5]-oxazocin-7-one **2a**. Its structure was confirmed by X-ray crystallographic analysis (Figure 3).

The ORTEP diagram of **2a** revealed that the double bond and sp^2 carbon atom of the carboxylic group forces the eight-member ring to adopt a boat conformation having minimum transannular nonbonded interactions within the ring. This preliminary discovery motivated us to improve the yield of cyclized compound **2a**. Accordingly, an increase in the catalyst loading of AgOTf up to 20 mol %, yielded **2a** in only 30% yield (Table 1, entry 6). When acid **1** was treated with AgOTf and K_2CO_3 in refluxing chloroform, the isolated yield of the compound **2a** increased up to 50% (Table 1, entry 7); a further increase in the quantity of AgOTf and K_2CO_3 up to 100 mol % did not improve the yield. When the cyclization of **1** was carried out with AgOTf (100 mol %) and K_2CO_3 (2 equiv) in chloroform under microwave irradiation at 100 °C for 20 min, an 85% conversion of starting material **1** into 8-*endo-dig* cyclized product **2a** was achieved (Table 1, entry 8). Even though desired compound **2a** was obtained in an excellent yield, a stoichiometric amount of AgOTf is required. Hence, effort toward the conversion of acid **1** into cyclized compound **2a** under the influence of a catalytic amount of silver or gold salt was carried out. Employment of a combination of strong base NaOH and AgOTf for cyclization of **1** under microwave irradiation resulted in cyclized product **2a** in only 32% yield (Table 1, entry 9). The use of $AgSbF_6$ in chloroform under reflux conditions resulted in zero conversion (Table 1, entry 10). Surprisingly, the excellent carbophilic gold salts such as AuCl and $AuCl_3$ with a combination of K_2CO_3 in acetonitrile by either conventional heating or microwave irradiation failed to yield compound **2a** (Table 1, entries 11–12). Utilization of PPh_3 as an additive in combination with a catalytic amount of AgOTf and K_2CO_3 under microwave conditions afforded **2a** in moderate yield (Table 1, entry 13). Similarly, combining AuCl with cocatalyst AgOTf and additive PPh_3 yielded compound **2a** in a trace amount (Table 1, entry 14). Furthermore, only 20% of product **2a** was obtained when Ag_2CO_3 was employed alone (Table 1, entry 15). Finally, the use of 10 mol % of AgOTf in the presence of K_2CO_3 (2 equiv) in toluene under microwave

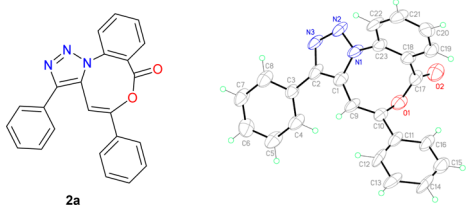


Figure 3. ORTEP diagram of compound **2a**.

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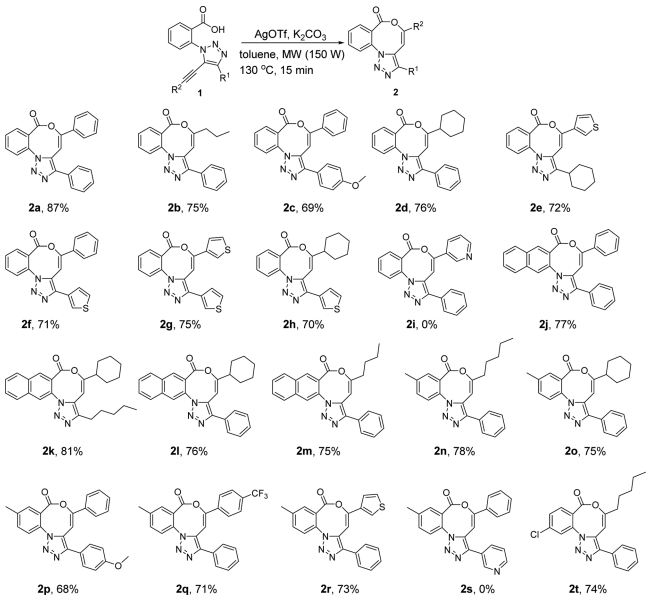
irradiation afforded cyclized compound **2a** in excellent yield (Table 1, entry 16).

To investigate the scope of this protocol, a variety of substituted acids **1** were prepared from substituted anthranilic acids **S1** and alkynes **S4**. The corresponding 8-*endo-dig* products **2** were obtained in excellent yields and the current protocol works well with aliphatic alkynes as well as with aromatic alkynes having electron-donating and -withdrawing groups on the phenyl ring (Scheme 1).

Scheme 1. Substrate Scope for the Synthesis of 1,2,3-Triazole-Fused-1,5,-Benzoxazocinones 2[a]

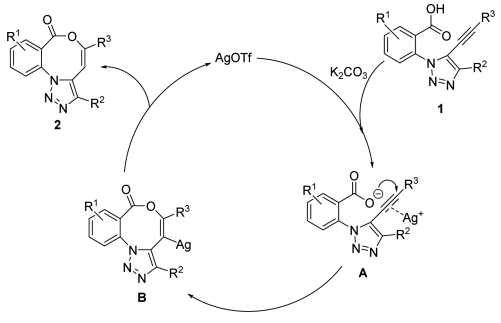


[a]Reaction conditions: **1** (0.27 mmol), AgOTf (10 mol %), K_2CO_3 (2 equiv), solvent (2 mL).

It is interesting to note that, in all cases, only 8-*endo-dig* cyclized products **2** were obtained. The structures of the products **2b**−**t** were confirmed by the two signals at 6−6.5 and ∼100 ppm respectively in the ^1H and ^{13}C NMR spectra.

The results suggested that activation of a C−C triple bond and the subsequent intramolecular addition of carboxylic acid were highly regioselective. In order to rationalize the regioselectivity in the cyclization of acid **1**, we propose a plausible mechanism in Scheme 2. In the first step, carbophilic AgOTf coordinates with the triple bond of acid **1**, which results in the enhancement of the electrophilicity of the alkyne.

Scheme 2. A Plausible Mechanism for AgOTf/K_2CO_3 Catalyzed Intramolecular Cyclization of Acid 1



Subsequent anti-*endo-dig* intramolecular nucleophilic attack by a carboxylate anion on Ag(I)-alkyne complex **A** forms **B**. Consequent protonolysis of the C−Ag bond of **B** produces 8-*endo-dig* product **2** with regeneration of AgOTf. The formation of highly regioselective 8-*endo-dig* intermediate **B** can be rationalized through the polarization effect exerted by the electron-withdrawing moieties present at the carbon of the alkyne (Figure 4).[14,15] In this case, electron-deficient triazole-

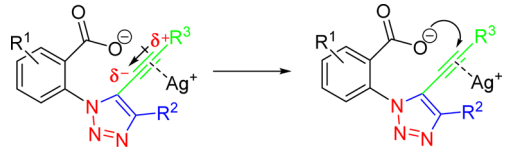


Figure 4. *Endo-dig* intramolecular nucleophilic addition via triazole-mediated polarization of alkyne.

mediated polarization of the alkyne increases the electrophilicity of the terminal carbon atom of the alkyne which facilitates *endo-dig* nucleophilic addition of the carboxylate anion to afford 8-*endo-dig* products **2**.

In conclusion, we have developed a synthetic protocol for the synthesis of novel 1,2,3-triazole-fused-1,5-benzoxazocinones **2** via a regioselective intramolecular cyclization of substituted ethynyl triazoyl benzoic acids **1**. The salient feature of this protocol involves the one-pot synthesis of crucial precursor 5-iodo-1,2,3-triazole benzoates **S5** from substituted 2-azido benzoic acid esters **S3** using the CuI/NBS catalytic system. The 5-iodo-1,2,3-triazole benzoates **S5** were further functionalized by a carbon−carbon triple bond through Sonogashira coupling with various terminal alkynes. Finally, the 1,4,5-substituted-1,2,3-triazole benzoic acids **1** were subjected to an intramolecular cyclization using AgOTf/K_2CO_3 to afford exclusively 8-*endo-dig* 1,2,3-triazole fused benzoxazocinones **2** in excellent yields.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00907.

Experimental procedures, characterization data, spectral data, and X-ray data for compound **2a** (PDF)
Crystallographic data (CIF)

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Notes

The authors declare no competing financial interest.

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