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Aust. J. Chem. **2011**, *64*, 1383–1389

A New Synthetic Protocol for One-Pot Preparations of 5-Halo-1,4-disubstituted-1,2,3-triazoles

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In this paper, a new synthetic protocol for one-pot preparations of 5-halo-1,4-disubstituted-1,2,3-triazoles is provided by rational combination of a Cu^I catalyzed azide–alkyne cycloaddition (CuAAC) reaction and an oxidative halogenation reaction. CuI- *N*-chlorosuccinimide (NCS) and CuBr-NCS reaction systems are developed, respectively, for effective preparations of 5-iodo-1,4-disubstituted-1,2,3-triazoles and 5-bromo-1,4-disubstituted-1,2,3-trizoles under mild conditions with a high tolerance of various sensitive groups.

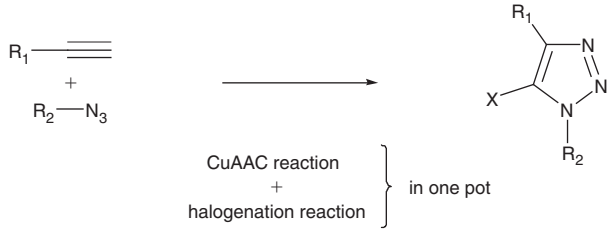
Manuscript received: 11 February 2011.
Manuscript accepted: 2 June 2011.
Published online: 23 August 2011.

Introduction

Recently, click chemistry has provided a simple method to build organic molecules in high yields under mild conditions in the presence of diverse functional groups.[1] The Cu^I catalyzed azide–alkyne cycloaddition (CuAAC) is considered a typical 'click' reaction in which a 1,2,3-triazole is formed in very high yields and good regioselectivity in the presence of Cu^I.[2,3] By now, the CuAAC reaction has been widely used in organic synthesis,[4,5] drug discovery,[6,7] molecular recognition,[8,9] bioconjugation chemistry,[10,11] and polymer and materials sciences.[12,13]

Aryl halides are important compounds in drug discovery and synthetic chemistry.[14] For example, aryl halides can act as reactants in several important synthetic transformations such as Heck reactions,[15] and Suzuki[16] and Negishi cross couplings.[17] Therefore, the combination of a CuAAC reaction and an halogenation reaction to prepare halo-1,2,3-triazoles would provide a novel synthetic protocol to produce structurally diverse functional 1,2,3-triazole molecules and promising drug candidates (Scheme 1).

Several methods have been reported for the preparation of 5-halo-1,4-disubstituted-1,2,3-triazoles: (1) specific 1,3-dipolar cylcoadditions between substituted alkynes and azides,[18–24] (2) substitution reactions based on the activity of 5-H in 1,2,3-triazoles,[25] (3) substitution by trapping the carbon anion intermediates,[26–28] (4) transformations from 5-NH_2-1,4-disubstituted-1,2,3-triazoles,[29] and (5) by-products from Cu^I-catalyzed Huisgen cycloaddition reactions.[30] But these methods often involve rigorous reaction conditions, lead to low yield or low chemo-selectivity, and in some cases the active halo-alkynes or alkynylboronates have to be prepared in advance. Recently, we found the CuI-*N*-bromosuccinimide (NBS) reaction system could promote a multi-component cycloaddition reaction to efficiently prepare 5-iodo-1,4-disubstituted-1,2,3-triazoles directly from azides and terminal alkynes.[27] In the CuI-NBS reaction system, NBS worked as an oxidant to oxidize I^- to I^+ in situ, and the I^+ produced in situ attacked the 5-carbon anion of the CuAAC reaction intermediate efficiently. Thus it is possible to combine the CuAAC reaction and halogenation reaction in one pot. In this paper, we analyze the potential demands of the oxidants in the combination of the CuAAC reaction and halogenation reaction. Through screening the oxidants, we develop a new more efficient CuI-*N*-chlorosuccinimide (NCS) reaction system for the one-pot preparation of 5-iodo-1,4-disubstituted-1,2,3-triazoles from azide and terminal alkynes. Moreover, NCS as an oxidant can be applied in effective one-pot preparations of 5-iodo-1,4-substituted-1,2,3-triazoles with the CuBr-NCS reaction system. Finally, a possible oxidation–reduction reaction mechanism is proposed to explain the high activities of NCS as oxidant in the CuX-NCS reaction systems in the preparation of 5-halo-1,4-disubstituted-1,2,3-triazoles.



Scheme 1. The preparation of 5-halo-1,2,3-triazole through the combination of Cu^I catalyzed azide–alkyne cycloaddition (CuAAC) reaction and halogenation reaction in one pot.

Results and Discussion

The One-pot Preparation of 5-Iodo-1,4-disubstituted-1,2,3-triazoles

In general, the direct iodination of an aromatic compound is a relatively difficult process because of the weak electrophilicity

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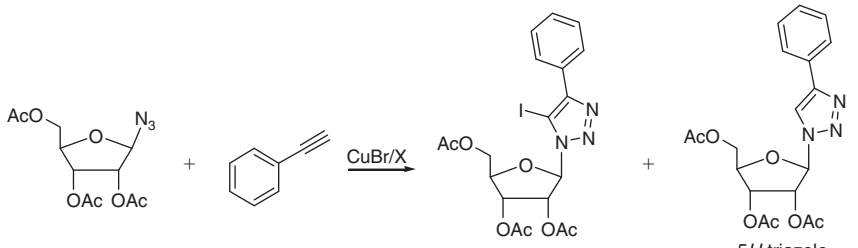
Table 1. The preparation of 5-iodo-1,4-disubstituted-1,2,3-triazole under different catalytic systems at ambient temperature



Entry	Copper(I)-Oxidant[A]	Reaction time [h]	Isolated yield **3a** (**4a**) [%]
1	CuI-$NaClO_2$	12	–
2	CuI-$NaNO_2$	12	–
3	CuI-$SnCl_4$	12	–
4	CuI-PCC	12	–
5	CuI-DDQ	12	10 (32)
6	CuI-IBD	12	20 (35)
7	CuI-NIS	12	30 (31)
8	CuI-NBS	5	85 (–)
9	CuI-NCS	3	92 (–)
10	CuI$(POCH_3)_2$-NCS	12	90 (–)
11	CuI$(PPh_3)_2$-NCS	12	90 (–)
12	CuI$(POCH_3)_2$-NBS	12	30 (15)
13	CuI$(PPh_3)_2$-NBS	12	37 (15)

[A]The mole ratio of alkyne, azide, CuI, and oxidant was 1.0 : 1.0 : 1.1, with 1.1 equiv. of *N*,*N*-diisopropylethylamine (DIPEA) added as the alkali.

of molecular iodine.[31] Several methods have been used to enhance the rate of the iodination reaction, with oxidative iodination reactions being one of the most effective methods. For example, NaI-$FeCl_3$,[32] $NaClO_2$/NaI,[33] air/I_2/$NaNO_2$,[34] and KI/*tert*-butyl hydroperoxide[35] reaction systems have been reported for the effective preparations of aryl iodide. In the oxidative iodination reaction, an iodine anion or iodine molecule is oxidized to I^+ in situ, and the active I^+ participates in electrophilic substitution reactions with aryl compounds more effectively. Therefore, the combination of an oxidative iodination reaction and a CuAAC reaction would provide an effective method for the one-pot preparation of iodo-1,2,3-triazole.

However, the Cu^+ salt in the combination reaction is easily oxidized because of the presence of an oxidant in the oxidative iodination reaction. If Cu^+ is oxidized to Cu^{2+}, it will lose its catalytic function for the 1,3-dipolar cylcoaddition between a terminal alkyne and azide. So the oxidant used in the combination reaction should be mild and selective enough to maintain effective oxidation of I^- to I^+, and at same time avoid the oxidation of Cu^+ to Cu^{2+}. Based on the above analysis, different oxidants were investigated in the CuI-oxidant reaction systems for the preparation of 5-iodo-1,4-substituted-1,2,3-triazoles (Table 1).

From the results in Table 1, the effect of oxidants on the distribution of products **3a** and **4a** are significant. With a strong oxidant like pyridinium chlorochromate (PCC), metal ion, and $NaNO_2$, neither 5-*H*-triazole **4a** nor 5-substituted-triazole **3a** is obtained. With a weak oxidant such as iodosobenzene diacetate (IBD), 5-*H*-triazole **4a** is the main product. The possible role of oxidant in the CuI-oxidant catalytic system is as follows. The oxidants in these reaction systems oxidize I^- into I^+ for

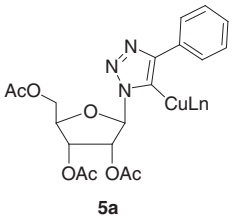
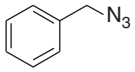
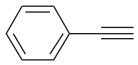
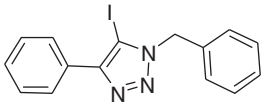
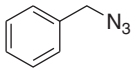
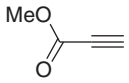
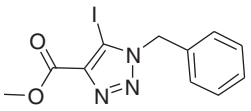
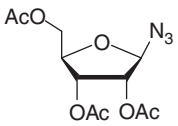
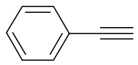
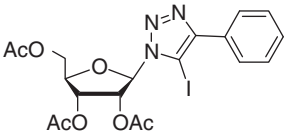
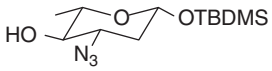
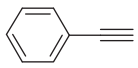
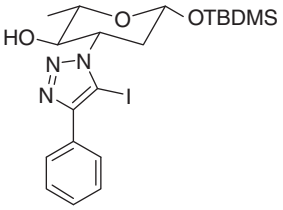
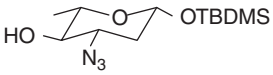
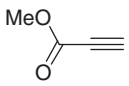
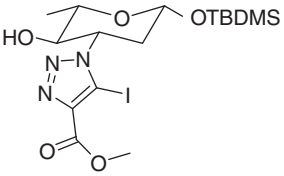
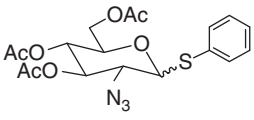
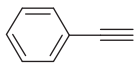
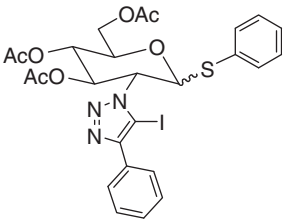
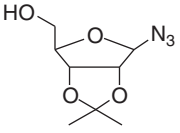
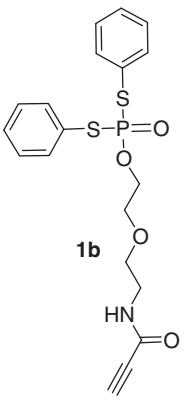
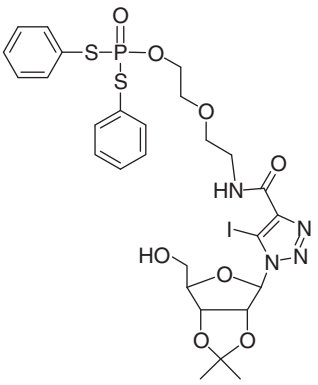


Fig. 1. The structure of carbon anion intermediate **5a** in the Cu^I catalyzed azide–alkyne cycloaddition (CuAAC) reaction.

efficiently trapping of the carbanion intermediate **5a** (Fig. 1), and lead to the formation of the 5-iodo-substituted products **3a**. If the oxidants cannot efficiently oxidize I^- to provide active I^+, the proton will attack the carbon anion intermediate **5a** to give more 5-*H*-triazole **4a** with a decrease of 5-substituted-triazole **3a**. If the oxidants are too strong, they will oxidize Cu^+ to Cu^{2+} with loss of catalytic capability for the CuAAC reaction, and then neither **3a** or **4a** can be obtained. Among all the oxidants in Table 1, NCS shows the best chemoselectivity, it can efficiently oxidize I^- to I^+ for trapping the carbon anion intermediate **5a** (Fig. 1) to give iodo-substituted product **3a**, and at the same time it can avoid the over-oxidation of Cu^+ and retain enough catalytic Cu^+ for the CuAAC reaction.

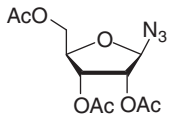
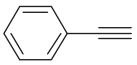
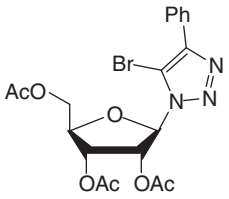
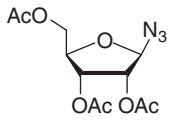
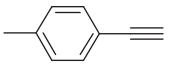
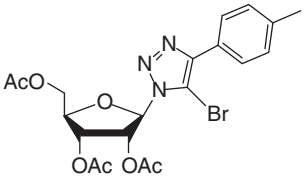
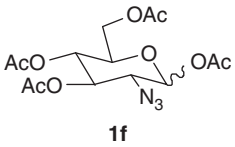
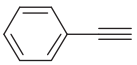
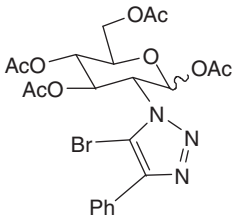
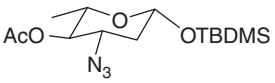
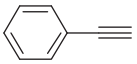
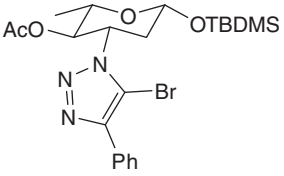
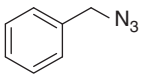
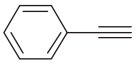
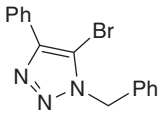
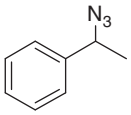
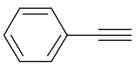
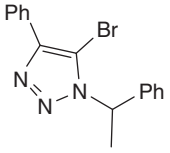
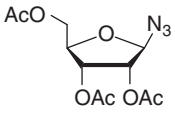
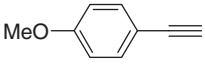
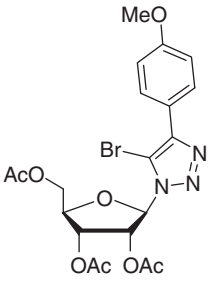
Other copper resources were also investigated for the combination of the oxidative iodination reaction and CuAAC reaction. Under the CuI$(POCH_3)_2$-NCS and CuI$(PPh_3)_2$-NCS reaction systems, 5-iodo-1,4-disubstituted-1,2,3-triazole **3a** was obtained with desirable yields within 12 h. But under the CuI$(POCH_3)_2$-NBS and CuI$(PPh_3)_2$-NBS reaction systems, low

Table 2. The preparations of 5-iodo-1,4-disubstituted-1,2,3-triazole mediated by CuI-*N*-chlorosuccinimide (NCS) reaction system

Entry[A]	Azide	Alkyne	Product	Time [h]	Isolated yield [%]
1	 **1b**	 **2a**	 **3a**	3	91
2	 **1b**	 **2b**	 **3b**	3	87
3	 **1a**	 **2a**	 **3c**	3	92
4	 **1c**	 **2a**	 **3d**	5	91
5	 **1c**	 **2b**	 **3e**	5	89
6	 **1d**	 **2a**	 **3f**	5	82
7	 **1e**	 **2c**	 **3g**		95

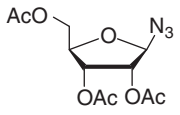
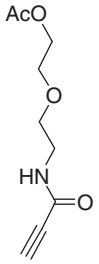
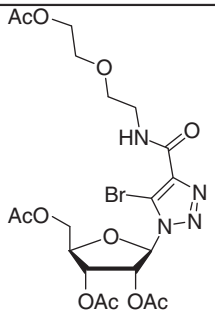
[A]The mole ratio of alkyne, azide, CuI, and oxidant was 1.0:1.0:1.1, with 1.1 equiv. of *N*,*N*-diisopropylethylamine (DIPEA) added as the base.

Table 3. The preparation of 5-bromo-1,4-disubstituted-1,2,3-triazoles mediated by CuBr-*N*-chlorosuccinimide (NCS) reaction system

Entry[A]	Azides	Alkynes	Products	Time [h]	Isolated yield [%]
1	 **1a**	 **2a**	 **6a**	8	81
2	 **1a**	 **2c**	 **6b**	8	76
3	 **1f**	 **2a**	 **6c**	8	71
4	 **1f**	 **2a**	 **6d**	13	65
5	 **1b**	 **2a**	 **6e**	10	70
6	 **1g**	 **2a**	 **6f**	12	65
7	 **1a**	 **2d**	 **6g**	12	60

(*Continued*)

Table 3. (Continued)

Entry[A]	Azides	Alkynes	Products	Time [h]	Isolated yield [%]
8	 **1a**	 **2e**	 **6h**	8	76

[A]The mole ratio of alkyne, azide, CuI, and oxidant was 1.5:1:1.5:1.5. with 1.1 equiv. of *N*,*N*-diisopropylethylamine (DIPEA) added as the base.

yields of **3a** were given within 12 h (entries 10–13 in Table 1). So, NCS showed higher activities than NBS as an oxidant in the CuI/ligand-oxidant reaction system for the one-pot preparation of 5-iodo-1,4-disubstituted-1,2,3-triazoles.

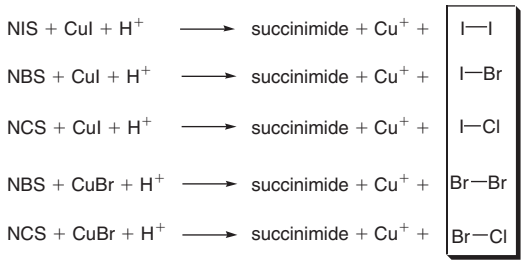
The application of this new synthetic protocol was then explored by using various azides and alkynes as building blocks to construct 5-iodo-1,4-disubstituted-1,2,3-triazole derivatives (entries 1–7 in Table 2). Different types of protective groups, such as acetyl, ketal, PhS-, and *tert*-butyldimethylsilyl (TBDMS) groups could tolerate the reaction conditions. Some widely used functional groups like ester, ether, and amide were also found to be intact under the CuI-NCS reaction system. Benzyl azides also successfully reacted with corresponding alkynes to give 5-iodo-1,4-disubstituted-1,2,3-triazoles in good to moderate yields (entries 1–2 in Table 2). Furthermore, the alkynes and azides in the sugar building blocks and cyclic adenosine 5″-diphosphoribose (cADPR) analogue were tried under the CuI-NCS catalytic system (entries 3–7 in Table 2), and the corresponding 5-iodo-1,4-substituted-1,2,3-triazoles were successfully obtained in good yields with intact sugar moieties.

The One-pot Preparation of 5-Bromo-1,4-disubstituted-1,2,3-triazoles

Based on the results obtained with the one-pot preparation of 5-iodo-1,4-disubstituted-1,2,3-triazoles, we applied NCS as the oxidant for the one-pot preparation of 5-bromo-1,4-disubstituted-1,2,3-triazoles (Table 3). Under CuBr-NCS reaction systems, terminal alkynes and azides can react smoothly at ambient temperature, and the target products 5-bromo-1,4-disubsituted-1,2,3-triazoles can be obtained in moderate to good yields with a wide tolerance of sensitive groups. Furthermore, the CuBr-NCS reaction system was also applied in the sugar building blocks and cADPR analogues, and the target compounds **6c**–**d** and **6h** were obtained with good yields.

The Possible Mechanism of the CuX-NCS for the One-pot Preparation of 5-Halo-1,4-disubstituted-1,2,3-triazoles

As oxidative halogenation reactions, the possible oxidation–reduction reactions between CuI and NIS, CuI and NBS, CuI and NCS, CuBr and NCS, and CuBr and NBS were proposed in the presence of proton (Scheme 2). Among all the oxidative products produced in situ from the reactions between CuI and NIS, NBS, and NCS, ICl should be the most active I^+ source, and thus the NCS-CuI reaction system should be most effective combination for the preparation of 5-iodo-1,4-disubstituted-1,2,3-triazole. For the bromination reaction, the BrCl species produced in situ should be the more active Br^+ source, and thus the NCS-CuBr reaction system should be the more effective combination for the preparation of 5-bromo-1,4-disubstituted-1,2,3-triazoles.

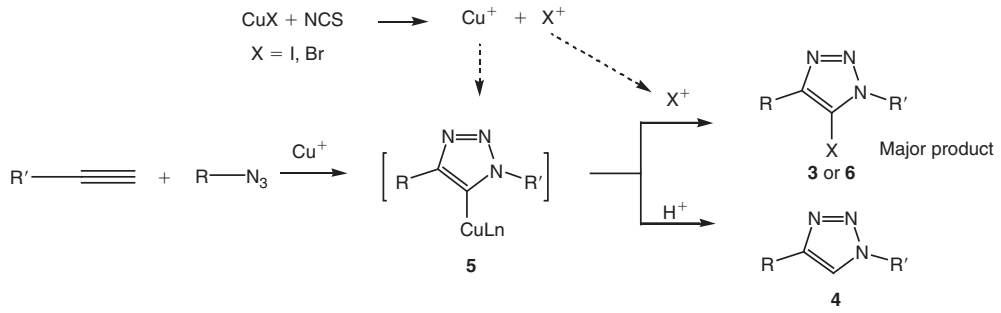


Scheme 2. The possible oxidation–reduction reactions between CuI and *N*-iodosuccinimide (NIS), CuI and *N*-bromosuccinimide (NBS), CuI and *N*-chlorosuccinimide (NCS), CuBr and NCS, and CuBr and NBS in the presence of proton.

Based on the above analysis about oxidative halogenation reactions and the mechanism of the CuAAC reaction in the literature,[4,5] a possible reaction mechanism of the CuX-NCS mediated azide–alkyne cycloaddition reactions is proposed (Scheme 3). There is a competitive reaction between 5-*H*-1,2,3-triazole and 5-halo-1,2,3-triazole. Protons attack the carbon anion intermediate **5** to produce 5-*H*-1,2,3-triazole, or X^+ attack the carbon anion intermediate **5** to produce 5-halogeno-1,2,3-triazole. In the CuX-NCS reaction system, X^- coming from CuX might be oxidized by NCS to provide an efficient X^+ source. With an efficient X^+ source, the halo-substitution reaction would be more competitive compared with proton-substitution, and thus the halo-substituted product **3** or **6** will be the major product in the competitive reaction procedure.

Conclusions

In this paper, we study CuX-oxidant systems for the preparation of 5-halo-1,4-disubstituted-1,2,3-triazoles by the combination



Scheme 3. The plausible mechanism of preparation of 5-halo-1,4-disubstituted-1,2,3-triazoles with CuX-*N*-chlorosuccinimide (NCS) reaction system.

of a CuAAC reaction and an oxidative halogenation reaction in one pot. CuI-NCS was developed as the most effective reaction system for the one-pot preparation of 5-iodo-1,4-disubstituted-1,2,3-triazoles using mild reaction conditions with a high tolerance of various sensitive groups. CuBr-NCS was developed as an effective reaction system for the preparation of 5-bromo-1,4-disubstituted-1,2,3-triazoles using mild reaction conditions. Successful application of the CuI-NCS and CuBr-NCS reaction systems in sugar and cADPR analogues illustrate the value of this method in the synthesis of designed biomolecules. A possible mechanism is proposed to explain the high activities of the CuI-NCS and CuBr-NCS reaction systems in the preparation of 5-halo-1,4-disubstituted-1,2,3-triazoles.

Experimental

Starting Materials

Compounds **1a** and **1c**–**g** were prepared according to the reported procedures.[36–38]

*General Procedure for Compounds **3a**–**g***

A mixture of **1** (0.035 mmol), **2** (0.048 mmol), CuI (10 mg, 0.053 mmol), *N*,*N*-diisopropylethylamine (DIPEA, 7 mg, 0.053 mmol), and NCS (7.5 mg, 0.058 mmol) in 3 mL of THF was stirred at room temperature. The reaction procedure was monitored by TLC. When the reaction was complete, the mixture was evaporated, and the residue was partitioned between ethyl acetate and H_2O. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and evaporated. The residue was purified by silica gel column chromatography to give compound **3**.

*General Procedure for Compounds **6a**–**h***

A mixture of **1** (0.048 mmol), **2** (0.072 mmol), CuBr (10 mg, 0.072 mmol), DIPEA (9 mg, 0.072 mmol), and NCS (9.5 mg, 0.072 mmol) in 3 mL of THF was stirred at room temperature. The reaction procedure was monitored by TLC. When the reaction was complete, the mixture was evaporated, and the residue was partitioned between ethyl acetate and H_2O. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and evaporated. The residue was purified by silica gel column chromatography to give compound **6**.

Compounds **3a**–**3g** and **6e** were identified using ^1H and ^{13}C NMR spectroscopy and electrospray ionization MS, and compared with the data in the literature.[22,25]

*Acetic Acid 4-Acetoxy-2-acetoxymethyl-5-(5-bromo-4-phenyl-[1,2,3]triazol-1-yl)-tetrahydrofuran-3-yl Ester (**6a**)*

δ_H (400 MHz, $CDCl_3$) 7.97–7.40 (m, 5H, ArH), 6.19–6.16 (m, 2H, H-1′, H-2′), 5.86 (dd, *J* 6.8, 4.8, 1H, H-3′), 4.53–4.50 (m, 1H, H-4′), 4.45 (dd, *J* 12.4, 3,2, 1H, H-5′a), 4.17 (dd, *J* 12.4, 3.2, 1H, H-5′b), 2.17, 2.15, 2.05 (3 × s, 9H, 3OAc). δ_C (100 MHz, $CDCl_3$) 169.7, 168.5, 168.4, 144.2, 128.1, 128.0, 127.8, 126.1, 107.8, 87.6, 80.3, 73.0, 70.1, 61.8, 19.8, 19.6. HRMS (ESI) Calc. for ($M + Na^+$) $C_{19}H_{20}BrN_3O_7Na$: 504.0382. Found: 504.0356 ($M + Na^+$).

*Acetic Acid 4-Acetoxy-2-acetoxymethyl-5-(5-bromo-4-p-tolyl-[1,2,3]triazol-1-yl)-tetrahydrofuran-3-yl Ester (**6b**)*

δ_H (400 MHz, $CDCl_3$) 7.89–7.31 (m, 4H, ArH), 6.20 (m, 2H, H-1′, H-2′), 5.88 (t, *J* 4.8, 1H, H-3′), 4.53–4.52 (m, 1H, H-4′), 4.48 (dd, *J* 12.4, 3.2, 1H, H-5′a), 4.20 (dd, *J* 12.4, 3.2, 1H, H-5′b), 2.44 (s, 3H, CH_3), 2.20, 2.18, 2.07 (3s, 9H, 3OAc). δ_C (100 MHz, $CDCl_3$) 169.7, 168.5, 144.3, 138.0, 130.8, 128.5, 126.0, 125.5, 125.2, 107.4, 87.5, 80.3, 73.0, 70.1, 61.8, 20.5, 19.8, 19.6. HRMS (ESI) Calc. for ($M + Na^+$) $C_{20}H_{22}BrN_3O_7Na$: 518.0539. Found: 518.0565 ($M + Na^+$).

*Acetic Acid 2,5-Diacetoxy-6-acetoxymethyl-3-(5-bromo-4-phenyl-[1,2,3]triazol-1-yl)-tetrahydropyran-4-yl Ester (**6c**). (α, β Isomers 1:1)*

δ_H (400 MHz, $CDCl_3$) 8.06–7.41 (m, 10H, ArH), 6.54 (d, *J* 3.2, 1H, H-1′), 6.53 (t, *J* 10, 1H), 6.37 (d, *J* 8.8, 1H, H-1′), 5.97 (t, *J* 10, 1H), 5.36–5.28 (q, *J* 10, 2H), 5.09 (dd, *J* 11.2, 3.2, 1H), 4.90 (t, *J* 9.6, 1H), 4.49–4.39 (m, 3H), 4.23–4.14 (m, 3H), 2.20–1.90 (m, 24H, 8OAc). δ_C (100 MHz, $CDCl_3$) 170.6, 169.8, 169.7, 169.2, 168.9, 168.3, 167.9, 128.9, 128.7, 126.8, 126.7, 109.1, 88.7, 72.9, 70.2, 68.6, 68.1, 61.3, 59.7, 29.7, 20.7, 20.6, 20.5, 20.3. HRMS (ESI) Calc. for ($M + H^+$) $C_{22}H_{25}BrN_3O_9$: 554.0774. Found: 554.0732 ($M + Na^+$).

*Acetic Acid 4-(5-Bromo-4-phenyl-[1,2,3]triazol-1-yl)-6-(tert-butyl-dimethyl-silany-loxy)-2-methyl-tetrahydropyran-3-yl Ester (**6d**)*

δ_H (400 MHz, $CDCl_3$) 8.01–7.41 (m, 5H, ArH), 5.32 (t, *J* 9.6, 1H, H-4′), 5.05 (dd, *J* 9.6, 1.6, 1H, H-1′), 4.85–4.78 (m, 1H, H-3′), 3.72–3.65 (m, 1H, H-5′), 2.78–2.70 (m, 1H, H-2′b), 2.40–2.36 (m, 1H, H-2′a), 1.92 (s, 3H, OAc), 1.32 (d, *J* 6.4, H-6′), 1.10 (s, 9H, $C(CH_3)_3$), 0.20, 0.18 (2 × s, 6H, $Si(CH_3)_2$). δ_C (100 MHz, $CDCl_3$) 168.0, 143.5, 128.5, 127.7, 126.1, 94.0, 73.1, 70.6, 58.1, 38.1, 24.8, 19.6, 17.1, 16.9, −5.0, −6.0. HRMS (ESI) Calc. for ($M + Na^+$) $C_{22}H_{32}BrN_3O_4SiNa$: 532.1243. Found: 532.1231 ($M + Na^+$).

*5-Bromo-4-phenyl-1-(1-phenyl-ethyl)-1H-[1,2,3]triazole (**6f**)*

δ_H (400 MHz, $CDCl_3$) 8.01–7.32 (m, 10H, ArH), 5.81 (q, *J* 7.2, 1H, CH), 2.14 (q, *J* 2.8, 1H, CH_3). δ_C (100 MHz, $CDCl_3$) 139.8, 129.7, 128.9, 128.5, 128.4, 128.3, 126.8, 126.4, 59.9, 21.8. HRMS (ESI) Calc. for ($M + H^+$) $C_{16}H_{15}BrN_3$: 328.0449. Found: 328.0477 ($M + H^+$).

*Acetic Acid 3,4-Diacetoxy-5-[5-bromo-4-(4-methoxy-phenyl)-[1,2,3]triazol-1-yl]-tetrahydrofuran-2-yl-methyl Ester (**6g**)*

δ_H (400 MHz, $CDCl_3$) 7.96–7.14 (m, 4H, ArH), 6.17–6.14 (m, 2H, H-1′, H-2′), 5.83 (dd, *J* 6.0, 4.8, 1H, H-3′), 4.52 (dd, 1H, *J* 7.2, 4.0, H-4′), 4.44 (dd, *J* 12.4, 3.6, 1H, H-5′a), 4.16 (dd, *J* 12.4, 3.6, 1H, H-5′b), 2.16, 2.14, 2.04 (3 × s, 9H, 3OAc). δ_C (100 MHz, $CDCl_3$) 169.7, 169.6, 168.5, 143.4, 128.0, 127.9, 124.3, 115.0, 114.8, 107.6, 87.6, 80.4, 73.0, 70.0, 61.8, 19.8, 19.6. HRMS (ESI) Calc. for ($M + Na^+$) $C_{19}H_{19}BrFN_3O_7Na$: 522.0288. Found: 522.0305 ($M + Na^+$).

*Acetic Acid 2-(2-{[5-Bromo-1-(3,4-diacetoxy-5-acetoxymethyl-tetrahydrofuran-2-yl)-1H-[1,2,3]triazole-4-carbonyl]-amino}-ethoxy)-ethyl Ester (**6h**)*

δ_H (400 MHz, $CDCl_3$) 7.45 (br, 1H, NH), 6.16–6.06 (m, 2H, H-1′, H-2′), 5.77–5.72 (m, 1H, H-3′), 4.50–4.49 (m, 1H, H-4′), 4.40 (dd, *J* 12, 4, 1H, H-5′a), 4.24–4.22 (m, 2H, H-1″), 4.16 (dd, *J* 2, 4, 1H, H-5′b), 3.70–3.65 (m, 6H, H-2″, H-4″,H-5″), 2.16, 2.11, 2.06 (3 × s, 9H, 3 × OAc). δ_C (100 MHz, $CDCl_3$) 170.1, 169.4, 168.5, 168.3, 157.7, 136.0, 127.9, 87.5, 86.6, 80.5, 72.9, 72.8, 70.0, 68.7, 68.1, 62.4, 61.8, 37.9, 20.0, 19.7, 19.5, 19.4. HRMS (ESI) Calc. for ($M + Na^+$) $C_{20}H_{27}BrN_4O_{11}Na$: 601.0757. Found: 601.0719 ($M + Na^+$).

Acknowledgements

This study was supported by the National Natural Sciences Foundation of China (grant no. 20802017) and Innovation Scientists and Technicians Troop Construction Projects of Henan Province (084100510002).

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