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Azidation *vs* [3 + 2]-cycloaddition: Chemoselective reaction of sodium azide towards *o*-alkynylaldehydes for the synthesis of *N*-heterocycles

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ABSTRACT

The chemoselective synthesis of functionalized azido- and triazolo-containing nitrogen heterocycles using sodium azide and *o*-alkynylaldehydes has been described. The azidation reaction was preferred in acetonitrile while the [3 + 2]-cycloaddition was favored in DMSO. Furthermore, the azido-pyranoquinolines were employed for the synthesis of benzonaphthyridines *via* the Staudinger reaction at room temperature.

Introduction

Organic azides are an important functional group for the synthesis of *N*-containing compounds due to their unique reactivity [1]. Their application in azide/alkyne [3 + 2]-cycloaddition and the Staudinger reaction unambiguously demonstrate their utility in various research fields [2]. Furthermore, the presence of the azide moiety in organic compounds can enhance their biological activities. Representative bioactive azido compounds include azidothymidine (AZT), azidocillin, and colecoxib derivatives (Fig. 1) [3].

The activation of unsaturated functionalities by polarised reagents such as halonium ions represents one of the most common strategies to prepare carbocycles and heterocycles [4,5]. In 2012, Zhu and co-workers reported iodo-triazole formation from azides and alkynes using NaI as an iodinating reagent (Scheme 1, i) [6]. Electrophilic cyclization reactions of *o*-alkynyl aldehydes using various nucleophiles have been previously reported (Scheme 1, ii) [4]; however, the application of azides as a nucleophile towards carbonyl centers remains challenging. Despite the availability of numerous methods for the synthesis of organic azides [7,8], the direct azidation [9] of carbonyl groups is rare. Considering our recent report [10], and our interest in alkynylaldehyde chemistry [11], herein we report the chemoselective azidation and [3 + 2]-cycloaddition of *o*-alkynylaldehydes using sodium azide (Scheme 1, iii).

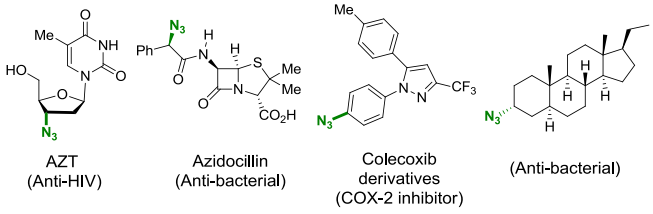

Figure 1. Representative azide-containing drugs.

Results and discussion

Optimization of the reaction conditions was achieved by initially examining the model reaction of 2-(*p*-tolylethynyl)quinoline-3-carbaldehyde **1a** in the presence of NaN_3 (2.0 equiv.), iodine (2.5 equiv.) and K_2CO_3 (2.5 equiv.), in acetonitrile at 70 °C for 0.5 h; the desired azidation product **2a** was obtained in 87% yield (Table 1, entry 1). Decreasing the amount of iodine and K_2CO_3 from 2.5 equiv. to 1.0 equiv. provided product **2a** in 48% yield (Entry 2). Next we increased the amount of K_2CO_3 to 2.5 equiv. keeping the amount of iodine unchanged which gave 40% yield of the desired product **2a** (Entry 3). Further, 2.5 equiv. of iodine with 1.0 equiv. of K_2CO_3 provided the azidated product **2a** in 50% yield (Entry 4). Among the various solvents screened for the reaction, DMSO and DMF provided triazole product **4a** in 26% and 20% yield, respectively (Entries 5–6). The use of methanol provided 1-azido-4-iodo-3-(*p*-tolyl)-1*H*-pyrano[4,3-*b*]quinoline[11c] **2a'** as the sole product (Entry 7). The reaction in the absence of both iodine and K_2CO_3 gave an increased yield of product

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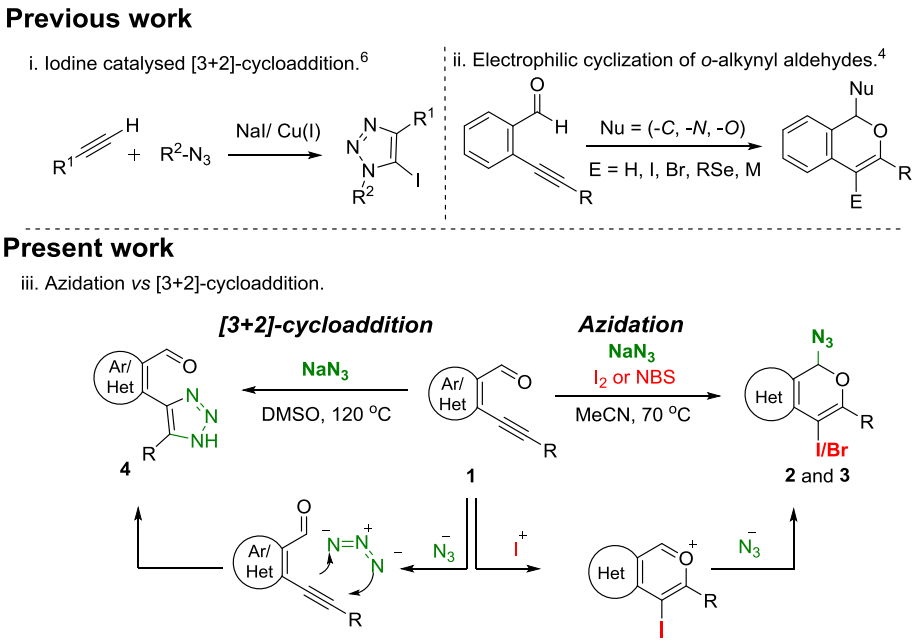
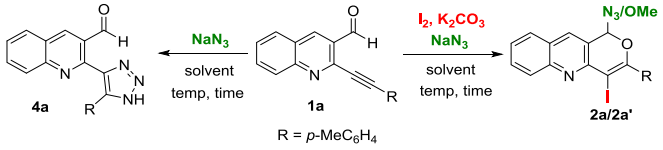
0040-4039/



Scheme 1. i) Triazole formation in the presence of NaI; ii) Electrophilic cyclization of *o*-alkynyl aldehydes with various (*C*-, *N*-, *O*-)[4] nucleophiles; iii) Chemoselective azidation *vs* [3 + 2]-cycloaddition.

Table 1
Optimization of the reaction conditions.[a,b]



Entry	NaN_3 (equiv.)	I_2 (equiv.)	K_2CO_3 (equiv.)	Solvent	Temp (°C)	Time (h)	Yield **2a** (%)[b]	Yield **4a** (%)[b]
1	**2.0**	**2.5**	**2.5**	**MeCN**	**70**	**0.5**	**87**	–
2	2.0	1.0	1.0	MeCN	70	6.0	48	–
3	2.0	1.0	2.5	MeCN	70	6.0	40	–
4	2.0	2.5	1.0	MeCN	70	6.0	50	–
5	2.0	2.5	2.5	DMSO	70	6.0	-[c]	26
6	2.0	2.5	2.5	DMF	70	6.0	-[c]	20
7	2.0	2.5	2.5	MeOH	70	6.0	–	-[d]
8	2.0	–	–	DMSO	70	6.0	–	56
9	2.0	–	–	DMSO	90	24	–	64
10	**2.0**	**–**	**–**	**DMSO**	**120**	**24**	–	**74**
11	2.0	–	–	MeCN	120	24	–	-[e]
12	1.5	–	–	DMSO	120	24	–	67
13	1.5	2.5	2.5	MeCN	70	0.5	80	–

[a] Reagents and conditions: **1a** (0.50 mmol), NaN_3, I_2, K_2CO_3, solvent (2.0 mL).
[b] Isolated yield.
[c] Trace amounts of **2a** was formed.
[d] 4-Iodo-1-methoxy-3-phenyl-1*H*-pyrano[4,3-*b*]quinoline was formed in 67% yield.
[e] Trace amounts of **4a** was formed.

4a (56%) at 70 °C for 6 h (Entry 8). An improvement in the yield was observed when the temperature was increased to 90 °C (Entry 9). Further increasing the temperature to 120 °C provided product **4a** in 74% yield (Entry 10). The reaction in MeCN provided product **4a** in trace amounts (Entry 11). Decreasing the amount of the azide source from 2.0 equiv. to 1.5 equiv. gave lower yields of product **4a** (Entry 12). Similarly, the yield of product **2a** was also lower with 1.5 equiv. of the azide source (Entry 13). On the basis of the above results, we concluded that iodine in acetonitrile was the best conditions for azidation (Entry 1). However, the absence of iodine in DMSO was suitable for the [3 + 2]-azide alkyne cycloaddition (Entry 10).

With the optimized reaction conditions in hand, we next explored the scope of the reaction for the synthesis of azido-iodo-pyranoquinolines **2a-k** and pyranopyridines **2l-m** using *o*-alkynylaldehydes **1a-m** possessing electron-releasing, electron-withdrawing, hetero-aromatic and aliphatic groups on the alkyne (Table 2). The reaction of substrates **1a-b** bearing *p*-Me- and *m*-OMe-substituted alkynes afforded the desired product **2a-b** in 87% and 85% yield, respectively (Entries 1 and 2). The structure of

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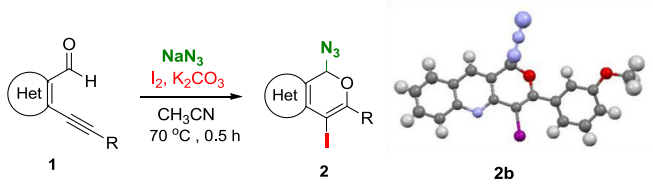
Table 2
Synthesis of azido-iodo-pyranoquinolines and pyranopyridines.[a,b]



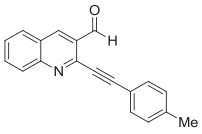
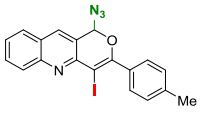
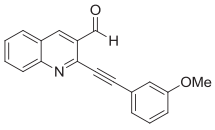
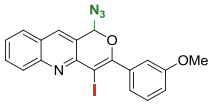
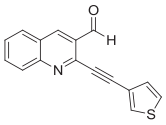
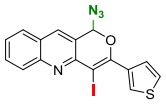
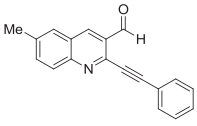
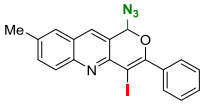
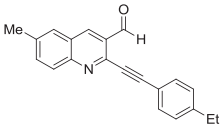
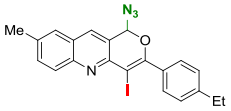
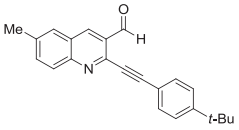
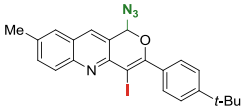
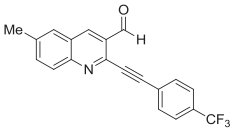
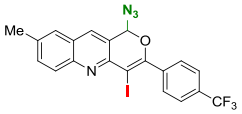
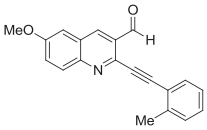
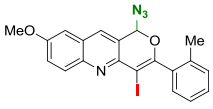
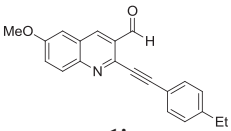
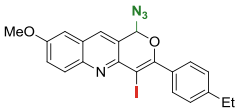
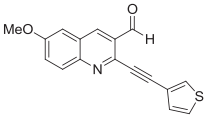
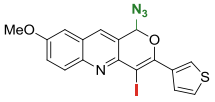
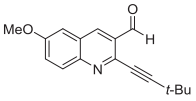
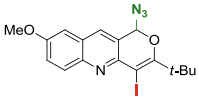
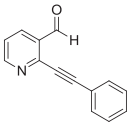
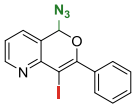
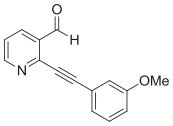
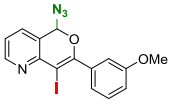
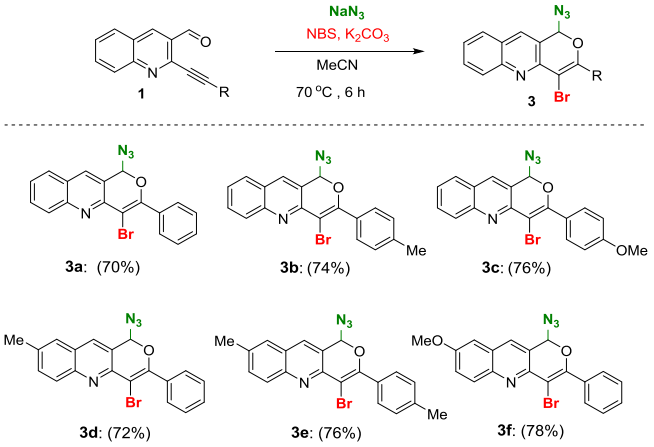
Entry	Substrate **1**	Product **2**	Yield (%)[b]
1	 **1a**	 **2a**	87
2	**1a**  **1b**	**2a**  **2b**	85
3	**1b**  **1c**	**2b**  **2c**	86
4	**1c**  **1d**	**2c**  **2d**	88
5	**1d**  **1e**	**2d**  **2e**	90
6	**1e**  **1f**	**2e**  **2f**	86
7	**1f**  **1g**	**2f**  **2g**	70
8	**1g**  **1h**	**2g**  **2h**	72

Table 2 (*continued*)

Entry	Substrate **1**	Product **2**	Yield (%)[b]
9	**1h**  **1i**	**2h**  **2i**	92
10	**1i**  **1j**	**2i**  **2j**	90
11	**1j**  **1k**	**2j**  **2k**	64
12[c]	**1k**  **1l**	**2k**  **2l**	85
13[c]	**1l**  **1m**	**2l**  **2m**	88
	1m	**2m**	

[a] Reagents and conditions: **1a** (0.50 mmol), NaN_3 (2.0 equiv.), I_2 (2.5 equiv.), K_2CO_3 (2.5 equiv.), solvent (2.0 mL).
[b] Isolated yield.
[c] Reaction time 12 h. CCDC No of product **2b** 1582016.



Scheme 2. Synthesis of azido-bromo-pyranoquinolines. [a]Reagents and conditions: **1** (0.50 mmol), NBS (2.5 equiv.), K_2CO_3 (2.5 equiv.), NaN_3 (2.0 equiv.), MeCN (2.0 mL), 70 °C, 6 h. [b]Isolated yield.

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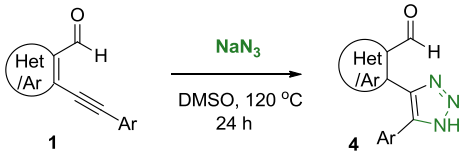
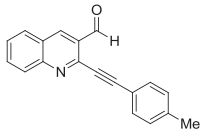
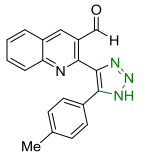
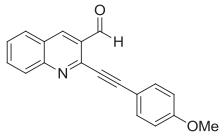
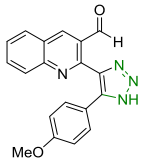
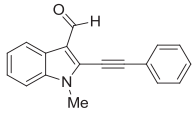
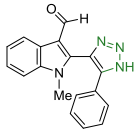
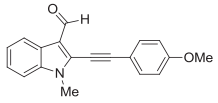
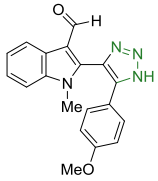
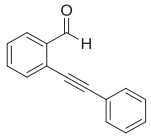
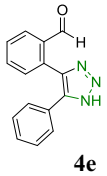
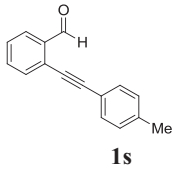
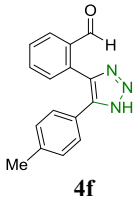
Table 3
Chemoselective [3 + 2]-cycloaddition reactions.



Entry	Substrate **1**	Product **4**	Yield (%)[b]
1	 **1a**	 **4a**	74
2	 **1o**	 **4b**	70
3	 **1p**	 **4c**	76
4	 **1q**	 **4d**	75
5	 **1r**	 **4e**	68
6	 **1s**	 **4f**	64

[a]Reagents and conditions: **1** (0.50 mmol), NaN_3 (2.0 equiv.), DMSO (2.0 mL), 120 °C, 24 h. [b] Isolated yield.

product **2b** was further confirmed by X-ray crystallographic studies. Electron rich thienyl alkyne **1c** gave the desired product **2c** in 86% yield (Entry 3). A similar reaction pattern was observed for **1d-f,** providing pyranoquinolines **2d-f** in high yields (Entries 4–6).

Highly electron-withdrawing alkynes such as 6-methyl-2-((4-(trifluoromethyl)phenyl)ethynyl)quinoline-3-carbaldehyde **1g** gave product **2g** in 70% yield (Entry 7). The sterically hindered alkyne **1h** gave product **2h** in 72% yield (Entry 8), while substrates **1i-j** gave products **2i** and **2j** in 92% and 90% yield, respectively (Entries 9 and 10). To our delight, the reaction of *o*-alkynyl aldehyde 2-(3,3-dimethylbut-1-yn-1-yl)-6-methoxy quinoline-3-carbaldehyde **1k** possessing an aliphatic alkyne gave product **2k** in 64% yield (Entry 11). Pyrido *o*-alkynyl aldehydes were also well tolerated and gave products **2l-m** in 85–88% yield (Entries 12 and 13).

After successful activation of the alkyne by molecular iodine, further attention was paid to the reactivity of *N*-bromosuccinamide as the halonium ion source for the synthesis of azido-bromo-pyranoquinolines **3** (Scheme 2). Alkynes possessing electron-neutral and electron-donating substituents gave product **3a-c** in 70–76% yield. Substrates with a functionalized quinoline ring afforded the desired products **3d-f** in moderate yields.

We next evaluated the scope of the [3 + 2]-azide alkyne cycloaddition reaction with various *o*-alkynylaldehydes for the synthesis of triazolyl compounds (Table 3). When the reaction was performed with quinoline *o*-alkynyl aldehydes **1** in DMSO at 120 °C, triazole substituted aldehydes **4a** and **4b** were obtained in 70–74% yield (Entries 1 and 2). Interestingly, the reaction conditions were suitable for the synthesis of triazole substituted aldehydes of *N*-methyl indole (**4c-d)** in moderate yields (Entries 3 and 4). The reactions of 2-(phenyl (**1r**) and *p*-tolyl (**1s**) ethynyl benzaldehydes gave the corresponding products **4e-f** in 68% and 64% yield, respectively (Entries 5 and 6).

After exploring the scope of the azidation and [3 + 2]-cycloaddition reactions, we further investigated the applicability of azidopyranoquinolines in the Staudinger reaction[12] (Scheme 3). Surprisingly the reactions of product **2**/**3** with PPh_3 in MeOH at room temperature gave benzonaphthyridines **6** instead of amine **5**.

A deuterium labeling experiment was performed in order to understand the reaction pathway for the formation of benzonaphthyridines **6** from azido-iodo-pyranoquinolines **2** (Scheme 4). The reaction of pyranoquinoline **2c** with PPh_3 in MeOD gave the deuterated product **6c'** in 82% yield with 87% incorporation of deuterium at the C-4 position. The presence of deuterium at the C-4 position suggests that tautomerization occurs in the reaction mechanism.

On the basis of the above results and our previous reports [10,11], a plausible mechanistic pathway was proposed (Scheme 5). The reaction was initiated by activation of the alkyne triple bond of *o*-alkynylaldehyde **1** by the electrophile (E^+) which was generated *in situ* by the reaction of K_2CO_3 and the halonium ion source (I_2/NBS) to form species **A** (Scheme 5a). Species **A** undergoes *6-endo-dig* cyclization to form oxonium ion **B**. Subsequently, nucleophilic addition of the azide anion gives the desired product **2/3**. In the Staudinger reaction [12] product **2/3** reacts with PPh_3 to give aza-ylide species **C** (Scheme 5b). This aza-ylide species **C** reacts with MeOD to give species **D** which upon tautomerization leads to the formation of species **E**. Attack of the nitrogen atom of species **E** on the carbonyl group affords betaine [13a] species **F** or **F'**. Benzonaphthyridine products **6** were formed from **F**/**F'** upon the liberation of triphenylphosphinoxide ($PPh_3 = O$)[13a] and methyl hypohalite (HOX) [13b-c] *via* attack of a methoxide anion.

Conclusion

In summary, we have demonstrated the chemoselective addition of NaN_3 to *o*-alkynyl aldehydes for the synthesis of azido-iodo pyranoquinolines and pyridines *via* electrophilic iodocyclization in acetonitrile and the formation of triazole products *via* [3 + 2]-cycloaddition in DMSO. We have also extended the application of the azidated products in the Staudinger reaction for the synthesis of benznaphthyridines through an aza-ylide intermediate.

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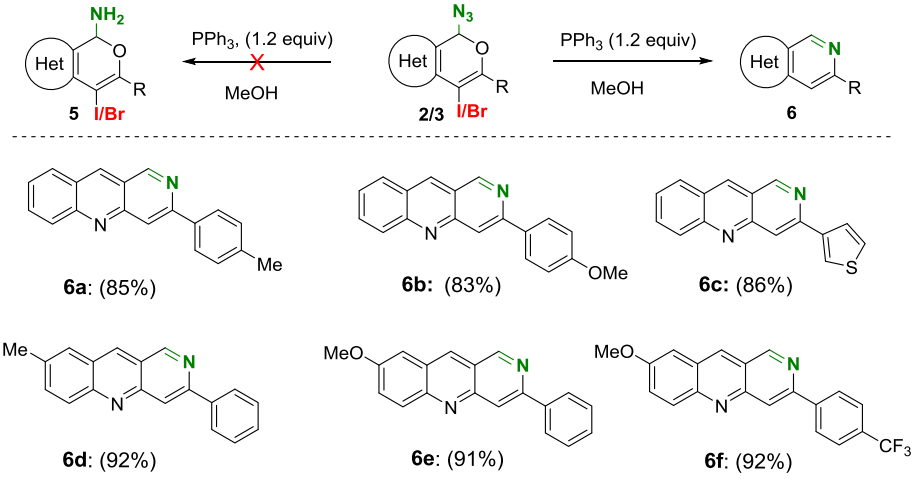
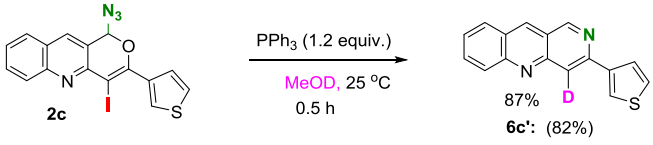
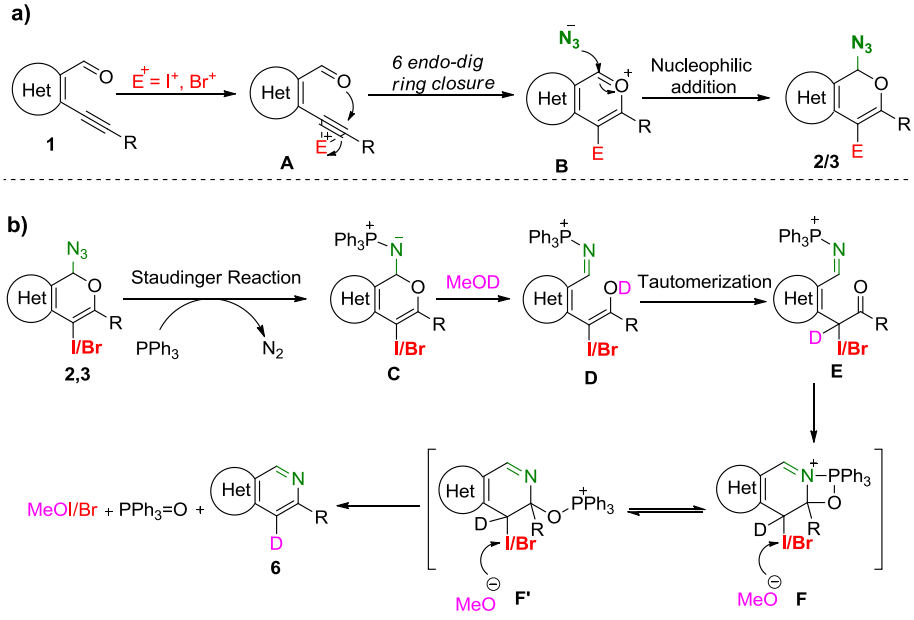


Scheme 3. Application of azido-halo-pyranoquinolines **2/3**. [a]Reagents and conditions: **2/3** (0.50 mmol), PPh_3 (1.2 equiv.), MeOH (2.0 mL,) 25 °C, 0.5 h. [b]Isolated yield.



Scheme 4. Deuterium labelling experiment.



Scheme 5. Proposed reaction mechanism.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2019.06.022.

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