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One-pot synthesis of N-fused 1,2,4-triazoles and related heterocycles via I<sub>2</sub>/TBHP-mediated oxidative C-N bond formation

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## Abstract

A metal-free iodine/TBHP-mediated oxidative C-N bond formation for the one-pot synthesis of *N*-fused 1,2,4-triazoles and related heterocycles *via* cyclization has been developed. This reaction which is amenable to scale-up affords the corresponding products with good to excellent yields and tolerates a wide range of functional groups.

Keywords: One-pot; 1,2,4-Triazoles; I<sub>2</sub>/TBHP; C-N bond formation.

## Introduction

1,2,4-Triazole-fused heterocycles are widely found in natural products and drugs with a broad spectrum of biological activities, such as antibacterial,<sup>1</sup> anti-HIV,<sup>2</sup> anti-inflammatory,<sup>3</sup> and antiepileptic activities,<sup>4</sup> (Fig. 1).



Figure 1. Selected biologically active 1,2,4-triazole-fused heterocycles

Various methods for synthesizing 1,2,4-triazole-fused heterocycles have been reported in the literature (Scheme 1). Vidavalur and co-workers reported a novel strategy to obtain *N*-fused 1,2,4-triazoles from iodobenzene and 2-hydrazinopyridines using molybdenum hexacarbonyl as a convenient and reliable solid source of carbon monoxide (Scheme 1, Method A).<sup>5</sup> Djuric and co-workers described the one step construction of 1,2,4-triazole-fused heterocycles from carboxylic acids and 2-hydrazinopyridine using a PS-PPh<sub>3</sub> resin combined with microwave heating (Scheme 1, Method B).<sup>6</sup> Zhang and co-workers reported a method to synthesize 1,2,4-triazole-fused heterocycles from *N*'-(pyridin-2-yl)benzohydrazide by dehydration in acetic acid under microwave irradiation at 180 °C.<sup>7</sup> Roberts and co-workers reported a mild *N*,*N*-carbonyldiimidazole (CDI) mediated cyclization reaction for the same transformation.<sup>8</sup> The oxidative cyclization of 2-(2-arylidenehydrazinyl) pyridines represents the most commonly used method for the synthesis of 1,2,4-triazole-fused heterocycles (Scheme 1, Method C). The oxidative cyclization of 2-(2-arylidenehydrazinyl) pyridines utilizing reagents such as hypervalent iodine,<sup>9</sup> chloramine T,<sup>10</sup> ceric ammonium nitrate,<sup>11</sup> and RuCl<sub>3</sub>/potassium peroxomonosulphate<sup>12</sup> or under mild electrolytic conditions<sup>13</sup> has been reported in the literature. However, there are some disadvantages to these methodologies, such as the use of toxic and metal reagents, as well as harsh reaction conditions.

Molecular iodine has widely been used in organic chemistry due to the advantages of being inexpensive and less toxic.<sup>14</sup> A number of methodologies using this reagent have been developed for the synthesis of heterocycles *via* carbon-heteroatom and carbon-carbon bond construction.<sup>15</sup> Herein, we report

an efficient  $I_2$ /TBHP-mediated one-pot protocol for the synthesis of 1,2,4-triazole-fused heterocycles in moderate to good yields.



Scheme 1. Synthesis of 1,2,4-triazole-fused heterocycles

## **Results and Discussion**

Initially, benzaldehyde (1a) and 2-hydrazinopyridine (2a) were chosen as model substrates for optimization of the reaction conditions. 2-Hydrazinopyridine (2a) was prepared in high yield by condensation of the corresponding aryl halide with hydrazine. The I<sub>2</sub>/tert-butyl hydroperoxide (TBHP) system has been widely reported in the literature for the construction of C-N bonds.<sup>16</sup> However, the desired product **3a** was formed in only 40% yield when the reaction was performed using  $I_2$  (0.2 equiv.) as a catalyst and TBHP (2 equiv.) as an oxidant in 1,4-dioxane at room temperature for 2 h (Table 1, entry 1). Several other catalysts such as KI, tetrabutylammonium iodide (TBAI), N-iodosuccinimide (NIS), CuI and PhI(OAc)<sub>2</sub> in the presence of TBHP (Table 1, entries 2–6) were tested, but they exhibited lower catalytic activities. Screening of the reaction temperature from 40 °C to 100 °C indicated that raising the temperature to 60 °C increased the yield of **3a** to 65 % (Table 1, entry 8), but raising the temperature to 80 °C and 100 °C had no further effect on the yield compared with 60 °C (Table 1, entries 9-10). Next, commonly used solvents were screened which revealed that using 1,4-dioxane afforded the best yield of 65% (Table 1, entries 11-15). To our surprise, when 1.0 equivalents of potassium carbonate (K<sub>2</sub>CO<sub>3</sub>) as a base was added to the reaction system, the desired product (3a) was obtained in 95% yield (Table 1, entry 18). Thus, the optimal reaction conditions were 1a (1 equiv.), 2a (1 equiv.), I<sub>2</sub> (0.2 equiv.), TBHP (2 equiv., 70% in water),  $K_2CO_3$  (1 equiv.) in 1,4-dioxane at 60 °C for 1 h (Table 1, entry 18).

		0 + N	NH <sub>2</sub>	Catalyst, Oxidant		N-N N	
	1a		2a			3a	
Entry	Catalyst	Oxidant	Base	Solvent	Temp	Time (h)	Yield <sup>b</sup>
	(equiv.)	(equiv.)	(equiv.)		(°C)		(%)
1	$I_2$	TBHP	—	1,4-dioxane	r.t.	2	40
2	KI	TBHP	—	1,4-dioxane	r.t.	2	25
3	TBAI	TBHP	—	1,4-dioxane	r.t.	2	Trace
4	NIS	TBHP	—	1,4-dioxane	r.t.	2	32
5	CuI	TBHP	—	1,4-dioxane	r.t.	2	20
6	PhI(OAc) <sub>2</sub>	TBHP	—	1,4-dioxane	r.t.	2	Trace
7	$I_2$	TBHP	—	1,4-dioxane	40	2	50
8	$I_2$	TBHP	—	1,4-dioxane	60	2	65
9	$I_2$	TBHP	—	1,4-dioxane	80	2	60
10	$I_2$	TBHP	—	1,4-dioxane	100	2	58
11	$I_2$	TBHP	—	EtOH	60	2	52
12	$I_2$	TBHP	—	H <sub>2</sub> O	60	2	30
13	$I_2$	TBHP	—	DMSO	60	2	45
14	$I_2$	TBHP	_	DCM	reflux	2	42
15	$I_2$	TBHP	—	EtOAc	60	2	48
$16^{c}$	$I_2$	TBHP	KI	1,4-dioxane	60	1	75
$17^{c}$	$I_2$	TBHP	KAc <sub>3</sub>	1,4-dioxane	60	1	82
<b>18</b> <sup>c</sup>	$I_2$	TBHP	K <sub>2</sub> CO <sub>3</sub>	1,4-dioxane	60	1	95
19 <sup>c</sup>	$I_2$	TBHP	Na <sub>2</sub> CO	1,4-dioxane	60	1	88

<sup>a</sup>Reagents and conditions: **1a** (1 mmol), **2a** (1 mmol), catalyst (0.2 mmol), oxidant (2 mmol), solvent (10 mL). <sup>b</sup>Isolated yield. <sup>c</sup>base (1.0 equiv.) was added to the reaction system.

With the optimized reaction conditions for C-N bond formation identified, the substrate scope was investigated to determine the generality of this method (Scheme 2). A series of substituted benzaldehydes with *ortho-, meta-* or *para-substituents* were explored and gave the desired 1,2,4-triazole-fused heterocycles (**3a-m**) in 72-95% yield. Compounds **3g**, **3i** and **3k** were also obtained in good yields, which indicated that the transformation is not affected by steric hindrance. However, the reaction of nitro-substituted substrates **3d**, **3l** and **3m** showed an obvious decrease in yield, which indicated that this reaction is affected by electronic factors and electron-withdrawing substituents are unfavorable. Moreover, cinnamic aldehyde and isobutyraldehyde can be converted into the corresponding 1,2,4-triazole-fused heterocycles in good yields. Next, we explored the substrate scope of 2-hydrazinopyridine and its derivatives (Scheme 3). Under the optimized reaction conditions, all substrates were converted into the desired 1,2,4-triazole-fused heterocycles (**3p-v**) in 92-97% yield. To our delight, the reaction performed on a 10 g (50 mmol) scale afforded **3a** in 94% yield, which indicated that the reaction is practical.

Scheme 2. Substrate scope for the synthesis of 1,2,4-triazole-fused heterocycles<sup>*a,b*</sup>

![](_page_4_Figure_0.jpeg)

<sup>a</sup> Reagents and conditions: 1 (1 mmol), 2 (1 mmol), I<sub>2</sub> (0.2 mmol), TBHP (2 mmol, 70% in water), K<sub>2</sub>CO<sub>3</sub> (1 mmol), 1,4-dioxane, 60 °C, 1 h; <sup>b</sup> Isolated yield.

**3n**, 90%

30, 91%

Scheme 3. Substrate scope for the synthesis of 1,2,4-triazole-fused heterocycles<sup>*a,b*</sup>

3m, 72%

![](_page_4_Figure_3.jpeg)

<sup>a</sup> Reagents and conditions: 1 (1 mmol), 2 (1 mmol), I<sub>2</sub> (0.2 mmol), TBHP (2 mmol, 70% in water), K<sub>2</sub>CO<sub>3</sub> (1 mmol), 1,4-dioxane, 60 °C, 1 h; <sup>b</sup> Isolated yield.

In order to explore the reaction mechanism, various control experiments were conducted. (E)-2-(2-Benzylidenehydrazinyl) pyridine was converted into the corresponding 1,2,4-triazole-fused heterocycle in 96% yield under the optimised reaction conditions (Scheme 4). When the reaction was

conducted in the presence of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) or butylated hydroxytoluene (BHT) as radical scavengers, compound **3a** was obtained in 93% and 91% yield, respectively, which indicated that the reaction did not proceed *via* a radical mechanism. When the reaction was conducted without TBHP, compound **3a** was obtained in only 22% yield. No desired product was detected when the reaction was performed without  $I_2$ , which indicated that  $I_2$  is necessary to this reaction and TBHP plays a supporting role.

![](_page_5_Figure_2.jpeg)

Based on our experimental results and previous investigations,<sup>17</sup> a plausible mechanism was proposed (Scheme 5). First, intermediate **A** was formed by the condensation reaction between benzaldehyde (1) and 2-hydrazinopyridine (2), then intermediate **B** was formed *via* a base-promoted oxidative iodination of **A**. Second, intermediate **B** underwent cyclization *via* nucleophilic substitution to obtain the desired intermediate **C**. Finally, intermediate **C** was deprotonated by the iodine anion and converted into compound **3a**. During the reaction, the eliminated HI was oxidized to I<sub>2</sub> by TBHP and the catalytic cycle was achieved.

Scheme 5. Proposed mechanism for the formation of 2a

![](_page_6_Figure_1.jpeg)

### Conclusion

In summary, we have developed an efficient one-pot synthesis of 1,2,4-triazole-fused heterocycles *via*  $I_2/TBHP$ -mediated oxidative C-N bond formation. This novel reaction works well with a wide range of substrates and can be conducted on gram scale.

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# Highlights

- 1, One-pot protocol for the synthesis of 1,2,4-triazole-fused heterocycles.
- 2, Wide substrate scope, short reaction time and high reaction yields.
- Acctebrace 3, The reaction can be conducted on gram scale.

# R<sup>1</sup>-CHO + $\sqrt{N}$ $M_2$ $\frac{I_2/TBHP/K_2CO_3}{I_4/diprage 60.9C Lb}$ $R^1$ $N_2$ $R^2$

metal fre gram-sca

igh vield

21 examples in 72-97% yields

4 An iodine/TBHP-mediated one-pot oxidative C-N bond formation for the synthesis of N-fused 1,2,4-triazoles and related heterocycles is developed.

1