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Regioselective halogenation of 2-substituted-1,2,3-triazoles *via* sp^2 C–H activation†

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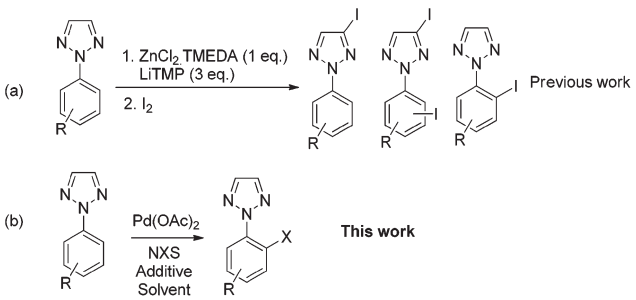
A highly regioselective halogenation of 2-substituted-1,2,3-triazoles was developed *via* sp^2 C–H activation. This method is compatible with halogen atoms, as well as electron-donating and electron-withdrawing groups. Meanwhile, the strategy is also efficient for the synthesis of a key intermediate of Suvorexant.

Aromatic halides, important starting materials utilized in complex structure and natural product syntheses, are extensively used in cross-coupling.[1] By far the most prevalent strategies for preparing aromatic halides are still the classic directed *ortho* lithiation, electrophilic aromatic substitution, and the Sandmeyer reaction.[2] However, these methods usually suffer from many limitations including poor regioselectivity, low yields, harsh reaction conditions, and tedious and dangerous reaction procedures. In the past decade, Pd(II)-catalyzed C–H halogenation utilizing directing groups has been studied extensively.[3] High yields and monoselectivities could be achieved with the assistance of some directing groups, including amides,[3a,e,i] pyridines,[3c,f,g] carboxylic acids,[3d] and oxazolines.[3h]

2-Substituted-1,2,3-triazoles, essential structural motifs in material science and medicinal chemistry (Fig. 1 Suvorexant and β3-AR agonist),[4] have unique chemical and structural properties. The synthesis and derivation of such compounds remain a challenge.[5] In 2012, Mongin for the first time reported a deproton-iodination of 2-substituted-1,2,3-triazoles.[6] However, this method was limited by a poor regioselectivity and a low yield, as well as harsh reaction conditions (Scheme 1a). Therefore, a general and practical method that enables the direct halogenation of 2-substituted-1,2,3-triazoles is of prime synthetic value. In this paper, we report on a palladium-catalyzed highly regioselective halogenation of 2-substituted-1,2,3-triazoles using NXS (X = Cl, Br, I) as halogenating reagents (Scheme 1b).



Scheme 1 Halogenation of 2-substituted-1,2,3-triazoles.

Based on the key contributions of Sanford and Ackermann,[7] the 2-phenyl-1,2,3-triazole (**1a**) and NBS (1.1 equiv.) reaction was initially selected to optimize the reaction conditions (Table 1). The reaction did not occur without the catalyst (Table 1, entry 1). At 100 °C, with $Pd(OAc)_2$ as a catalyst and no additive added, *ortho*-bromination product **2a** was obtained with 31% yield, and no reaction occurred in position 4 or 5 of the triazole cycle. When PivOH (1.0 eq.) was added, the yield increased to 88%. The yield increased to 90% (Table 1, entry 4) when the reaction was performed with half the amount of PivOH (0.5 eq.). No evident yield improvement was achieved by increasing the catalyst loading to 10 mol% (Table 1, entry 5). By contrast, when the catalyst loading was decreased to 3 mol %, the yield was reduced to 79% (Table 1, entry 6). $Pd(OAc)_2$ seemed to be an efficient catalyst for this transformation, and other palladium species such as $Pd(TFA)_2$, $PdCl_2$ and $Pd(PPh_3)_4$ were tested and found to be substantially less

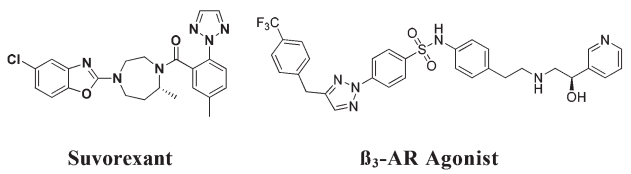


Fig. 1 Present medicines containing 2-substituted-1,2,3-triazoles.

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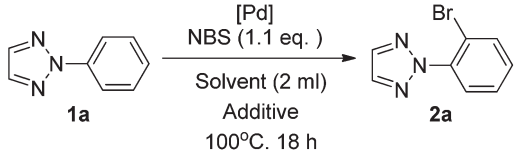
Table 1 Optimization of the bromination conditions[a]



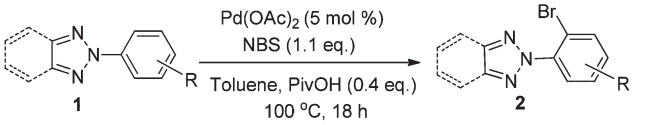
Entry	Catalyst	Additive (eq.)	Solvent	Yield[b] (%)
1			Toluene	
2	$Pd(OAc)_2$	PivOH (0)	Toluene	31
3	$Pd(OAc)_2$	PivOH (1)	Toluene	88
4	$Pd(OAc)_2$	PivOH (0.5)	Toluene	90
5[c]	$Pd(OAc)_2$	PivOH (0.5)	Toluene	92
6[d]	$Pd(OAc)_2$	PivOH (0.5)	Toluene	79
7	$Pd(TFA)_2$	PivOH (0.5)	Toluene	55
8	$PdCl_2$	PivOH (0.5)	Toluene	20
9	$Pd(PPh_3)_4$	PivOH (0.5)	Toluene	Trace
10	$Pd(OAc)_2$	TFA (0.5)	Toluene	55
11	$Pd(OAc)_2$	AcOH (0.5)	Toluene	50
12	$Pd(OAc)_2$	TsOH (0.5)	Toluene	67
13	$Pd(OAc)_2$	MsOH (0.5)	Toluene	56
14	$Pd(OAc)_2$	CF_3SO_3H (0.5)	Toluene	45
15	$Pd(OAc)_2$	PivOH (0.5)	DCE	73
16	$Pd(OAc)_2$	PivOH (0.5)	CH_3CN	61
17	$Pd(OAc)_2$	PivOH (0.5)	Dioxane	55
18	$Pd(OAc)_2$		AcOH	86

[a] Reaction conditions: **1a** (0.5 mmol), NBS (0.55 mmol), $Pd(OAc)_2$ (0.025 mmol), additive (0.25 mmol), solvent (2.0 mL), stirred at 100 °C over 18 h. [b] Isolated yields. [c] $Pd(OAc)_2$ (0.05 mmol). [d] $Pd(OAc)_2$ (0.015 mmol).

effective (Table 1, entries 7–9). An acidic additive was proven to be essential for this reaction. Some additives such as PivOH, TFA, AcOH, TsOH, MsOH, and CF_3SO_3H were screened among which PivOH gave the best result in this reaction. Compared with other solvents (DCE, CH_3CN, dioxane and AcOH), toluene was the most suitable for this reaction (Table 1, entries 15–18).

Under the optimized conditions, the scope of 2-substituted-1,2,3-triazoles bearing diverse substituents on the arene ring was examined (Table 2). Electron-rich substituents, such as methyl and methoxyl, were well tolerated, resulting in the formation of the desired products in high yields (Table 2, entries 2 and 3). Other electron-deficient substrates bearing the ester group, a potential second chelating group, could undergo bromination in moderate yields (Table 2, entries 4 and 5). Notably, bromination occurred at the less sterically hindered *ortho*-position in moderate yields for substrates bearing substituents in the *meta* position (Table 2, entries 5, 6, and 7). The inclusion of potential reactive groups such as halogen atoms (Table 2, entries 7, 8, and 11) further highlighted the functional group compatibility of this catalytic system. Moreover, expanding the scope from the phenyl to the naphthyl system facilitated the formation of the 2-position bromination product with 83% yield (Table 2, entry 9). An additional aromatic ring on the 2-substituted-1,2,3-triazoles was tolerated as well, and bromination occurred efficiently (Table 2, entries 10 and 11). Notably, when 1.1 equivalent of NBS was added to the reaction system, only monohalogenation occurred, but the presence of excess NBS could result in a good di-bromination product yield (Table 2, entry 12). The bromination of 1-substituted-1,2,3-triazoles (1 m) did not occur under identical conditions (Table 2, entry 13).

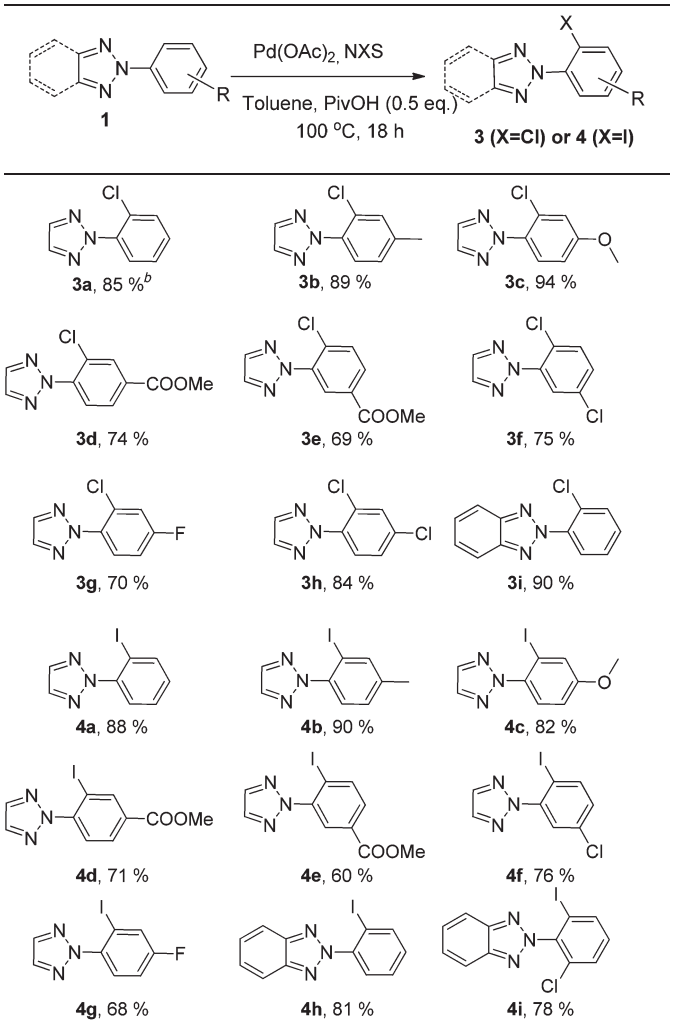
Table 2 *ortho*-Bromination of 2-substituted-1,2,3-triazoles[a]



Entry	1	Product (2)	Yield[b] (%)
1	1a	2a	90
2	1b	2b	94
3	1c	2c	91
4	1d	2d	77
5	1e	2e	69
6	1f	2f	70
7	1g	2g	68
8	1h	2h	70
9	1i	2i	86
10	1j	2j	97
11	1k	2k	74
12[c]	1a	2l	70
13	1m	2m	

[a] Reaction conditions: **1a** (0.5 mmol), NBS (0.55 mmol), $Pd(OAc)_2$ (0.025 mmol), PivOH (0.25 mmol), toluene (2.0 mL), stirred at 100 °C over 18 h. [b] Isolated yields. [c] 2.2 eq. NBS was used.

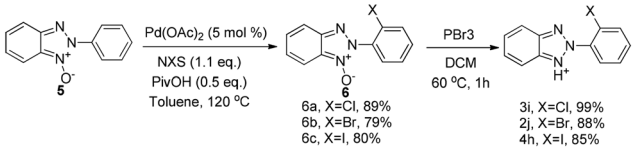
Table 3 *ortho* Chlorination and iodination of **1**[a]



[a] Reaction conditions: **1a** (0.5 mmol), NBS (0.55 mmol), $Pd(OAc)_2$ (0.025 mmol), PivOH (0.25 mmol), toluene (2.0 mL), stirred at 100 °C over 18 h. [b] Isolated yields.

We then investigated the chlorination and iodination of 2-substituted-1,2,3-triazoles under similar reaction conditions (Table 3). Similar to the *ortho*-bromination described above, we used the catalytic system in the *ortho*-chlorination for most of the 2-substituted-1,2,3-triazoles, despite which *ortho*-iodination remained efficient. Electron-rich and electron-withdrawing groups in the *para* or *meta* positions of the aromatic ring were well tolerated, resulting in good to moderate yields of the desired products. However, substituents in the *meta* position facilitated chlorination, and iodination still occurred at a less sterically hindered *ortho*-position with moderate yield. Good tolerance to the chemically active functional groups was also revealed. For example, halogen atoms and ester groups on substrates remained after the palladium-catalyzed reaction. Another aromatic phenyl group on the triazoles was also tolerated.

Additionally, we examined the possibility of performing the *ortho*-halogenation of 2-substituted-1,2,3-triazole *N*-oxides (Scheme 2). The *ortho*-halogenation of *N*-oxide **5** was sluggish

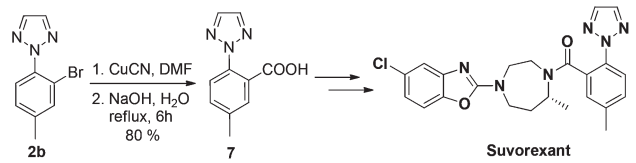


Scheme 2 Halogenation of 2-substituted-1,2,3-triazole *N*-oxides.

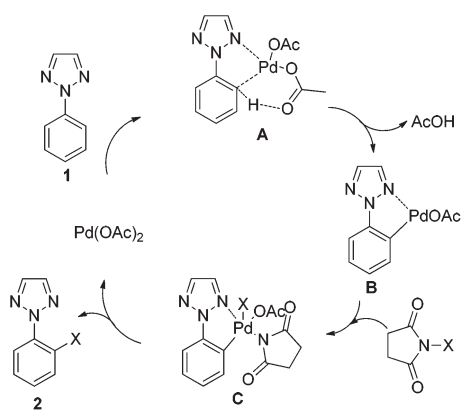
under otherwise identical conditions. At an increased reaction temperature (120 °C), we observed excellent yields of monohalogenated products (**6**). Notably, only mono-halogenated products were obtained even when 2.2 equivalents of halogenating reagents were added to the reaction system. The second *ortho*-halogenation was completely inhibited, which is presumably attributed to the steric interactions between the oxygen atom in the $N-1$ position and the halogen atom. Compounds (**6**) were readily deoxygenated and halogenated 2-substituted-1,2,3-triazoles were produced using typical methods in high yields.

The application of transition-metal-catalyzed C–H functionalization in the synthesis of medicinal compounds remains a challenge.[8] The synthesis of compound **7**, a part of the existing Suvorexant pharmacophore,[9] previously depended on the copper-catalyzed amination of 2-iodo-5-methylbenzoic acid. The high cost, low regioselectivity, and tedious purification for isomer removal limit the rapid synthesis of Suvorexant.[10] Currently, 2-substituted-1,2,3-triazoles **2b** can be readily converted to compound **7** through simple synthetic operations (Scheme 3).[11]

Based on our results and previous studies on the palladium-catalyzed halogenation of aromatic compounds,[7,12] we proposed a catalytic cycle for the halogenation of 2-substituted-1,2,3-triazoles (Scheme 4). First, 1,2,3-triazole **1** is



Scheme 3 Synthesis of precursor **7** of Suvorexant.



Scheme 4 Plausible reaction mechanism.

coordinated with $Pd(OAc)_2$ to form cyclopalladated intermediate **A**. The presumed participation of acetate in aromatic proton abstraction to generate an intermediate **B** is followed by the addition of NXS to form **C**. Finally, subsequent reductive elimination occurs, yielding the *ortho*-halogenated product **2** and the regenerated Pd^{II} catalyst.

In summary, the first example of a palladium-catalyzed *ortho*-halogenation of 2-substituted-1,2,3-triazoles *via* C–H activation was developed. This catalytic system is compatible with the halogen atom, as well as with electron-rich and electron-withdrawing groups. The unprecedented reaction provides potential access to valuable structures for drug discovery and materials science.

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