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Cite this: *New J. Chem.*, 2021, **45**, 3969

Facile and direct halogenation of 1,2,3-triazoles promoted by a KX–oxone system under transition metal free conditions†

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Received 20th October 2020,
Accepted 27th January 2021

DOI: 10.1039/d0nj05170e

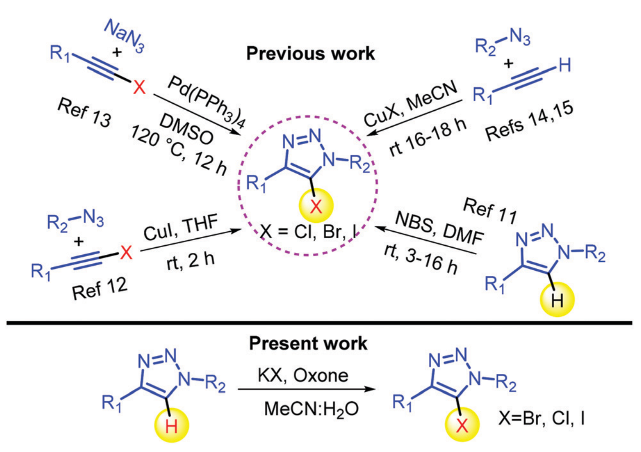
rsc.li/njc

A convenient and efficient oxidative halogenation of 4-aryl 1,2,3-triazoles is realized at ambient temperature under transition metal free conditions. In this methodology, halogenation is achieved by using readily available potassium halides (KBr, KCl, and KI) with oxone as an oxidant under mild reaction conditions and halogenated products are obtained in good to excellent yields. In addition, the synthesized halogenated triazoles are applied for the synthesis of functionalized molecules.

Introduction

Metal mediated reactions are usually not preferred because the contamination of metals is a serious issue in pharmaceutical and related industries. Owing to the increased emergence of atom economy and user-friendly strategies, a variety of metal free synthetic methods have been developed for the construction of C–C and C–hetero bonds *via* cross coupling reactions. Among them, the C–H bond functionalization in heterocyclic systems is fundamentally challenging in modern organic synthesis and is of paramount importance owing to the presence of heterocyclic scaffolds in a variety of medicinally and biologically active molecules.[1] Interestingly, 1,2,3-triazoles and their derivatives are associated with unique chemical and structural properties. These heterocycles have been extensively investigated and have found applications in biological science,[2] pharmaceuticals,[3] agrochemicals, materials science[4] and so on.[5] Among the various derivatives, 5-halo-1,2,3-triazoles are considered as valuable structural units[6] for further chemical transformations[7] and biological activities.[8] Owing to the ever-increasing importance of 5-halo-1,2,3-triazole compounds, various approaches for their synthesis have been developed in the recent years.[9] Unfortunately, direct halogenation on the 1,2,3-triazole ring achieved limited success using reactive halogenating agents.[10] We found only one report from the L. L. Kong[11] group on the direct halogenation of 1,2,3-triazoles by reacting with *N*-halosuccinimides for long reaction time (Scheme 1).

Nevertheless, the metal mediated Huisgen cycloaddition reaction has also contributed to the synthesis of halo triazoles (Scheme 1). For instance, the Fokin and Hein group[12] reported the CuI catalysed selective synthesis of 5-iodo-1,4,5-trisubstituted-1,2,3-triazoles by using iodoalkynes and organic azides. The Kuang[13] group also observed the formation of bromo triazole when bromo alkyne was made to react with sodium azide in DMSO with Pd $(PPh_3)_4$ at 120 °C for 12 h during the controlled experiments of their study. Similarly, Vidal[14] and G. Zhang[15] research groups independently demonstrated a multi component reaction for the synthesis of 5-halo-1,2,3-triazoles from alkynes and azides in the presence of copper halides with different bases and additives. Despite these remarkable advances in metal mediated reactions, generally applicable methods for the metal free synthesis of halo substituted 1,2,3-triazoles are still desirable.



Scheme 1 Synthesis of halogenated 1,2,3-triazoles.

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† Electronic supplementary information (ESI) available: Experimental section, ^1H and ^{13}C-NMR spectral data, and copies of NMR spectra. See DOI: 10.1039/d0nj05170e

Fascinatingly, the HX–oxidant system has drawn special attention in recent years as an inexpensive, non-metallic, and readily available system for oxidative halogenation reactions. Oxidative halogenation is well known for its high fidelity as a potential alternative tool for hazardous molecular halogens, providing experimental simplicity and good selectivity for various organic transformations. Despite several oxidants[16] being reported for the oxidation of halide ions, there is still a need for developing much safer and greener approaches in the field of heterocyclic systems. Although, 5-halo triazoles are synthesized *via* metal mediated azide alkyne cycloaddition reactions, a more atom-economical and practically viable approach is, however, represented by oxidative halogenation to triazoles under metal free conditions. In continuation of our strategies for developing C–H functionalizations[17] on electron rich systems, herein, we disclosed a general, rapid, and operationally simple oxidative halogenation to obtain differently substituted triazoles. The process is promoted by a KX–oxone system under ambient conditions.

Results and discussion

The initial survey of experiments was directed towards finding the optimized reaction conditions, which included a broad array of oxidants and solvents as shown in Table 1.

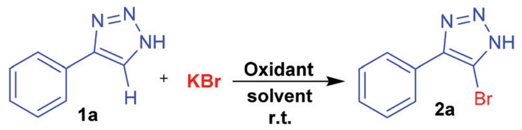
In the beginning, the halogenation of 4-phenyl-1,2,3-triazole **1a** was carried out using KBr with several oxidants in aq. acetonitrile. The reactions of **1a** and KBr with aq. H_2O_2 and aq. TBHP at ambient temperature for 2 h gave the expected product 5-bromo-4-phenyl-1*H*-1,2,3-triazole **2a** in low yields (Table 1, entries 1 and 2). Similar reactions using $PhI(OAc)_2$ and $K_2S_2O_8$ as oxidants furnished product **2a** in good yields (Table 1, entries 3 and 4). To our delight, the use of oxone as an oxidant under similar reaction conditions was fruitful and furnished the desired product **2a** in an excellent yield (96% Table 1, entry 5). Thus, we then continued exploring the solvent medium using oxone as an oxidant. Accordingly, subsequent reactions using aq. DMSO and aq. MeOH as solvents led to the formation of product **2a** in moderate yields (Table 1, entries 6 and 7). In a similar way, the relatively non-polar solvents such as toluene, hexane, dichloroethane and tetrahydrofuran in aqueous medium were not successful and produced the corresponding brominated product **2a** in moderate yields (Table 1, entries 8–11). Interestingly, water as solvent underwent bromination under reflux conditions and gave the corresponding brominated product **2a** in 78% yield (Table 1, entry 12). Based on the above reactions, aq. acetonitrile as solvent medium at ambient temperature appeared to be the best. We then continued to investigate other halide sources for the present halogenation reaction. The halide sources such as LiBr, NaBr and TBAB were not efficient and led to the formation of **2a** in moderate to low yields (Table 1, entries 13–15).

Furthermore, when the halide source was changed from metal salts to aq. hydrobromic acid, we found that the desired product was obtained in low yield (Table 1, entry 16). Additionally, we found the decrease in yield of **2a** when the quantity of KBr is increased (Table 1, entries 17 and 18). After screening of several oxidizing agents and solvents, we found that the best reaction conditions are substrate **1a** with KBr (1.1 equiv.) and oxone (1.1 equiv.) in acetonitrile:H_2O for 2 h at room temperature. Having these optimized reaction conditions in hand, we continued to explore the substrate scope and their results are tabulated in Table 2. The cumene substituted triazole gave the corresponding brominated product **2b** in excellent yield. Triazoles bearing halogens furnished the corresponding brominated products **2c**, **2d**, **2e** and **2f** under optimized conditions in very good yields. Triazoles containing electron withdrawing groups like $-NO_2$ and –CN underwent smooth conversion to afford the desired products **2g**, **2h** and **2i** in good yields. The naphthyl substituted triazole also afforded product **2j** in 88% yield. Thiophene substituted triazole also afforded the corresponding brominated product **2k** in very good yield (91%) under the present reaction conditions. Interestingly, triazoles with methyl and benzyl substituents on N also furnished the desired brominated products **2l** and **2m** in 74% and 72% yield, respectively.

Similarly, triazoles with ketone and ester functional groups were also brominated successfully to afford the corresponding products **2n** and **2o** in moderate yields. Unfortunately, the hydroxy methyl substituted triazole under optimised conditions did not produce the corresponding brominated product **2p** and the starting material was isolated unaffected.

Encouraged by the above results of bromination, we then changed our attention towards investigating the substrate scope for chlorination reactions using potassium chloride (KCl) as a chlorinating agent under optimal reaction conditions.

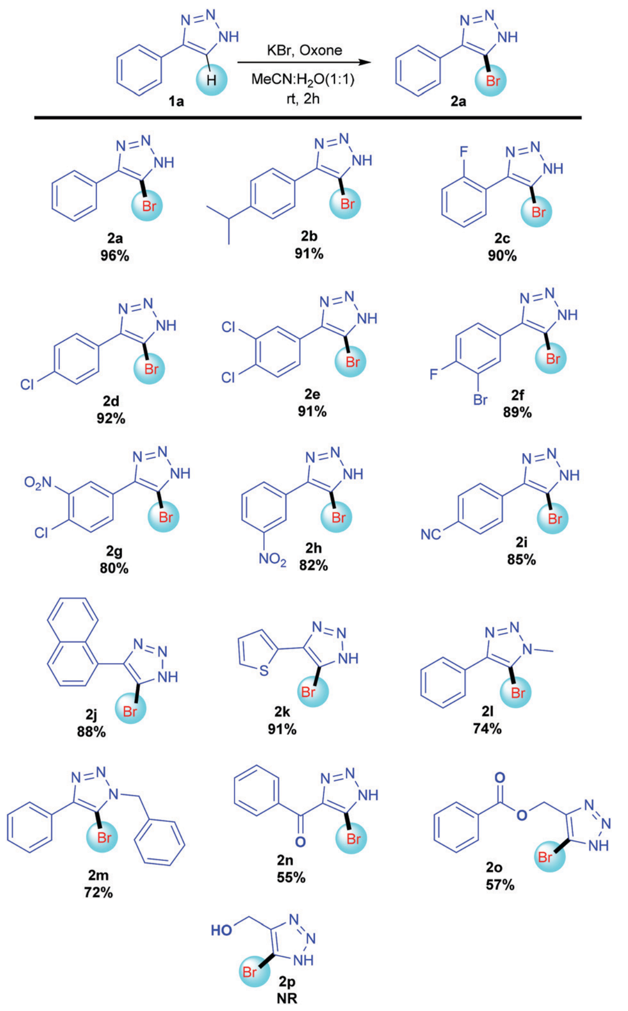
Table 1 Optimization of reaction conditions[a]



Entry	Solvent : H_2O (1 : 1)	Oxidant (1.1 eq.)	MX (1.1 eq.)	Yield[b] (%)
1	MeCN : H_2O	H_2O_2	KBr	25
2	MeCN : H_2O	Aq. TBHP	KBr	32
3	MeCN : H_2O	$PhI(OAc)_2$	KBr	82
4	MeCN : H_2O	$K_2S_2O_8$	KBr	69
5	**MeCN : H_2O**	**Oxone**	**KBr**	**96**
6	DMSO : H_2O	Oxone	KBr	45
7	MeOH : H_2O	Oxone	KBr	32
8	Toluene : H_2O	Oxone	KBr	65
9	Hexane : H_2O	Oxone	KBr	50
10	DCE : H_2O	Oxone	KBr	45
11	THF : H_2O	Oxone	KBr	58
12	H_2O	Oxone	KBr	78
13	MeCN : H_2O	Oxone	LiBr	65
14	MeCN : H_2O	Oxone	NaBr	32
15	MeCN : H_2O	Oxone	TBAB	28
16	MeCN : H_2O	Oxone	Aq. HBr	45
17	MeCN : H_2O	Oxone	KBr (1.5 eq.)	86
18	MeCN : H_2O	Oxone	KBr (2.0 eq.)	20

[a] All reactions were carried out by using triazole **1a** (1 equiv.), MX (1.1 equiv.) with oxidant (1.1 equiv.) in solvent : H_2O (2 mL) for 2 h at room temperature. [b] Isolated yields based on triazole **1a**.

Table 2 Substrate scope on bromination of 1,2,3-triazoles[a]



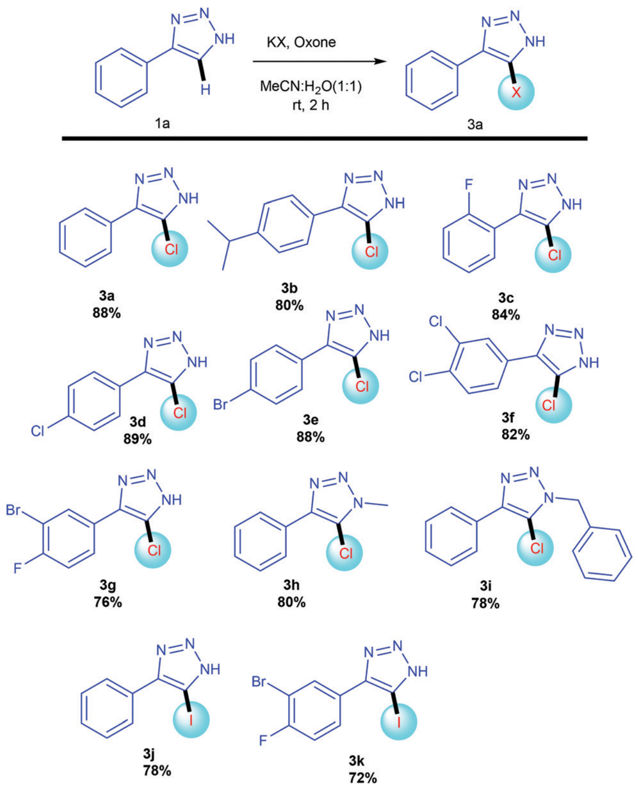
[a] All reactions were carried out by using triazole **1a** (1 equiv.), KBr (1.1 equiv.) with oxone (1.1 equiv.) in aq. acetonitrile (1 : 1, 2 mL) for 2 h at room temperature. NR = no reaction.

Chlorination of aryl triazoles was also successful and the corresponding results are shown in Table 3.

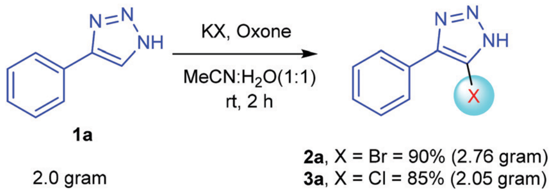
The reactions of phenyl and cumene substituted triazoles with potassium chloride under optimal reaction conditions gave chlorinated products **3a** and **3b** in good yields. Halogen substituted aryl triazole derivatives furnished the corresponding products **3c**, **3d**, **3e**, **3f** and **3g** in good yields. Similarly, triazoles bearing methyl and benzyl substituents on N also produced the desired products **3h** and **3i** in good yields under optimized reaction conditions. In addition to the above, iodinated triazoles **3j** and **3k** were also synthesized in good yields under the optimised reaction conditions.

To check the performance of present halogenation on a large scale, we carried out the reactions in a 2.0 g scale as shown in Scheme 2. Accordingly, both bromination and chlorination reactions proceeded well furnishing the desired halogenated products in very good yields. Thus, these reactions indicate the practical applications of the present method on a large scale.

Table 3 Substrate scope on chlorination and iodination of aryl-1,2,3-triazole[a]



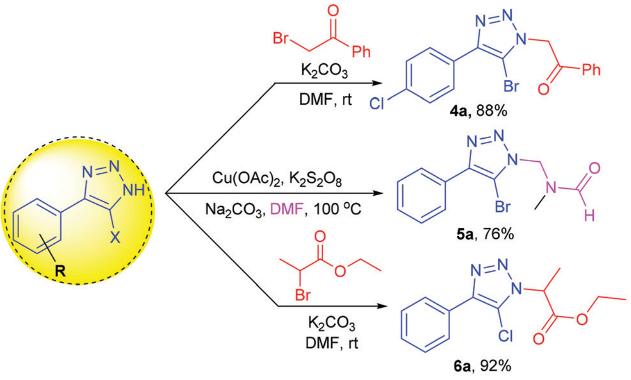
[a] All reactions were carried out by using triazole **1a** (1 equiv. 0.44 mmol), KX (1.1 equiv.) and oxone (1.1 equiv.) in aq. acetonitrile (1 : 1, 2 mL) at room temperature for 2 h.



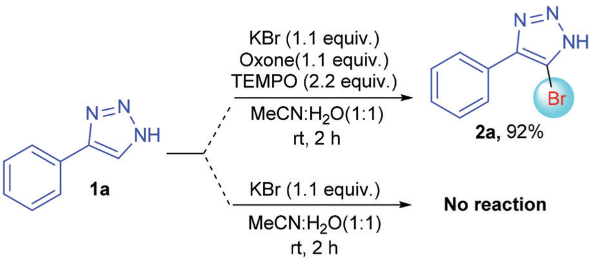
Scheme 2 Gram scale experiment.

To demonstrate the synthetic applications of the synthesized products, a few transformations were carried out. When compound **2d** was treated with phenacyl bromide using potassium carbonate in DMF at room temperature, the corresponding product **4a** was obtained in 88% yield. Similarly, **2a** was made to couple with DMF under the oxidative C–H functionalization strategy using Cu(OAc)$_2$ and $K_2S_2O_8$ at 100 °C. This reaction produced the desired product **5a** in 76% yield. Furthermore, **3a** was also subjected to reaction with 2-bromo ethyl propionate in the presence of potassium carbonate in DMF at room temperature to furnish the desired product **6a** in 92% yield (Scheme 3).

To understand the mechanism of the reaction, we performed controlled experiments as shown in Scheme 4.

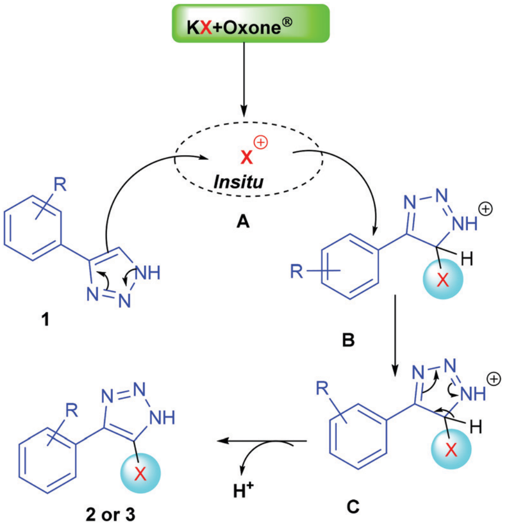


Scheme 3 Transformations of halogenated triazoles.



Scheme 4 Controlled experiment.

The bromination reaction was carried out in the presence of a radical scavenger 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) in order to check the possibility of the radical mechanism. However, this reaction displayed almost no effect and the corresponding halogenated product was obtained in very good yields. Thus, these experiments suggest that the present oxidative halogenation might not be proceeding through the radical mechanism. In addition, as expected the present halogenation in the absence of an oxidant did not proceed and the starting material was isolated unaffected. This reaction indicates that an oxidizing agent is necessary for the present halogenation reaction. Thus, based on the above controlled experiments and literature precedence,[18] we believe that the combination of KX and oxone results in the formation of an electrophilic X^+ species which further takes part in the reaction to furnish the desired halogenated substituted triazoles as shown in Scheme 5.



Scheme 5 Tentative reaction mechanism.

Conclusions

A mild and convenient method for the oxidative halogenation of aryl-1,2,3-triazoles under transition metal free conditions is developed. The success of this method lies in the use of readily available and inexpensive KX (potassium halides) as a halide source and oxone as an oxidant. The present method furnished a variety of halogenated aryl-1,2,3-triazole derivatives in a short reaction time in very good yields. The present reaction represents considerable advancement over previously reported halogenation of aryl-1,2,3-triazoles and is a straightforward approach for halogenation without the use of toxic molecular halogens. We demonstrated successfully the practical feasibility of the present strategy by scaling up the reaction quantity. Furthermore, the synthesized products are transformed into functionalised molecules in good yields.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

The authors thank DST-INSPIRE (DST/INSPIRE Fellowship/2017/IF70456), New Delhi, India, for financial support.

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