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A highly practical and convenient halogenation of fused heterocyclic *N*-oxides

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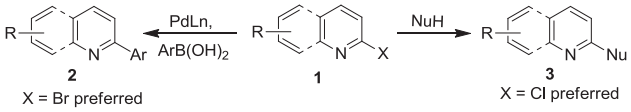
ABSTRACT

A novel, simple and practical method for the regioselective halogenation of fused heterocyclic *N*-oxides has been developed. It employs Vilsmeier reagent, generated in situ by POX_3 and DMF, as both the activating agent and the nucleophilic halide source. The method is amenable across a broad range of substrates, including quinolines, isoquinolines and the diazine *N*-oxides, possessing a variety of substitution patterns. Furthermore, all of the reagents associated are cheap and easy to obtain. The potential extension of this method to a one-pot oxidation/halogenation sequence that obviates the need for isolation of the *N*-oxide intermediates is also presented.

1. Introduction

N-heterocycles are prevalent in biologically active molecules and are increasingly attractive scaffolds in the development of new pharmaceuticals. As a kind of very important N-heterocycles, quinoline, isoquinoline and their derivatives have always been research focus of organic synthetic chemists, material science chemists and pharmaceutical chemists. Pharmacological studies have demonstrated that the quinoline and isoquinoline rings system have a broad range of biological activities, such as anticancer,[1] antiviral,[2] antibacterial,[3] antifungal,[4] anti-inflammatory[5] and antiplatelet aggregation.[6] To introduce functional group at the carbon atom adjacent to nitrogen atom (C2 position) is a challenging task for organic synthetic chemists. Toward this purpose, a novel strategy for Pd-catalyzed C2-H direct functionalization from azine *N*-oxides have been developed,[7] but these methods have not found wide application, most likely due to extra N—O reduction step and excess *N*-oxides starting material is needed to achieve good yields. Since halogen can be easily transformed into other functional groups due to the development of coupling reactions (**1** to **2**, Scheme 1) and the nucleophilic aromatic substitutions (**1** to **3**, Scheme 1), seeking for reliable synthetic methods for C2-halogenation belongs to an area with general interest.[8] Unfortunately, direct incorporation of halogens onto heterocycles proves challenging, as issues of poor regioselectivity and over halogenation often arise.[9] Instead, halogenation of the corresponding *N*-oxides (readily available via oxidation of the parent arenes) offers a popular solution.



Scheme 1. Common derivatization methods for *N*-heteroarenes.

Traditionally, the 2-chlorination[10] or bromination[11] of heteroarenes are accomplished by treating *N*-oxides **5**, or 2-hydroxy heteroarenes **6**, prepared from **5** in hot acetic anhydride, with POX_3 (or with PPh_3/NBS for **7b**[12]) at elevated temperature, sometimes PX_5 is added to facilitate the reaction (Scheme 2A). Although these two routes are widely used, significant drawbacks are associated. The direct halogenation employing POX_3 suffers from poor regioselectivity (halogenation at C2- and C4- position) and low yield is observed for the conversion of **5** to **6**, although halogenation with **6** usually provides high yield. Besides, large quantity of POX_3 is required in both methods. $POCl_3$ is toxic and lots of attention needs to be taken in quenching the reaction with water, and the situation becomes worse in kilogram scale reactions. In addition, exposure of *N*-oxides to prolonged heating can cause safety concerns regarding thermal stability and the liability of exothermic degradation.

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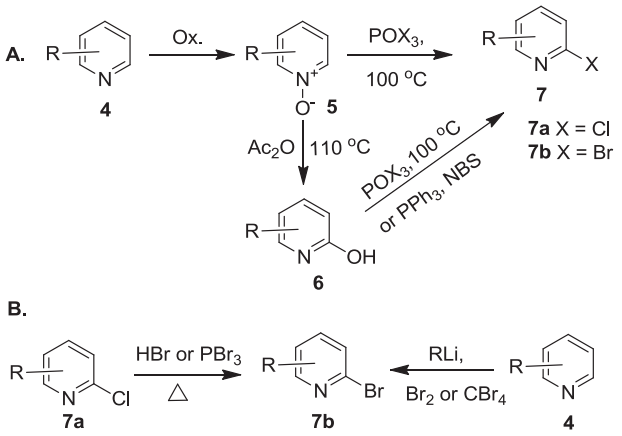
Alternatively, the 2-bromo heterocycles **7b** can also be prepared by direct bromination under metalation conditions with **4**,[13] or halogen exchange reaction with **7a** (Scheme 2B).[14] However, only a limited number of substrates are suitable for these two methods most likely due to the strong acidic or basic conditions associated.



Scheme 2. Traditional methods for *N*-oxides halogenation.

The 2-bromo heteroarenes came to our attention during our efforts to prepare large quantities of a key intermediate for a drug candidate. The 2-chloro heteroarene substrate affords much lower yield than the 2-bromo analogue does. Indeed, it is well known that aromatic bromines exhibit much better reactivity than the corresponding aromatic chlorines in metal catalyzed cross-coupling reactions. Beyond their interest as synthetic intermediates, bromo group is present in numerous drugs and frequently encountered in biologically active products in particular of marine origin (hymenialdisine, lamellarins). Further, recent structural studies have pointed specific interaction that can be established by bromo group in ligand-protein complexes.[15] The recent understanding of these effects will probably stimulate the incorporation of this group in potentially bioactive compounds.

Recently, Baran and co-workers developed a good method for C2-bromination of N-heterocycles employing tosic anhydride as the activator and tetra-*n*-butylammonium bromide (TBAB) as the nucleophilic bromide source.[16] The regioselectivity of their developed method is excellent. However, the method is not practical for kilogram production because it requires a very dilute condition (0.01 M) in order to achieve the good yield for most cases. Besides, both tosic anhydride and TBAB cost too much in kilogram production. Therefore, development of practical, mild and reliable methods for *N*-oxide bromination is demanded.

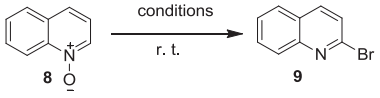
In previous communications,[17] we reported a simple, mild and scalable method for the synthesis of 2-chloro quinolines and isoquinolines, from the corresponding *N*-oxide precursors and Vilsmeier reagent, which was generated in situ by $POCl_3$ and DMF. More recently, Guo and co-workers have achieved the chlorination of quinoline *N*-oxides and isoquinoline *N*-oxides using PPh_3 and Cl_3CCN in refluxing toluene, but no bromination products could be detected in their attempt using several commonly brominating agents.[18] Encouraged by our previous achievement in the C-2 chlorination of *N*-oxides, we rationalized that, application of Vilsmeier reagent with the bromide counteranion, our methodology may serve as an effective means to directly synthesize the desired brominated products in a single step under mild conditions.

2. Results and discussion

Since all of the known activating reagents for *N*-oxides belong to electrophiles, screening those strong electrophiles with bromide source became our strategy. To access the feasibility, we initiated a reaction optimization study with quinoline-*N*-oxide (Table 1). Unfortunately, none of those reagents gave satisfactory result. No reaction was detected for BBr_3 or TMSBr (entries 1–2), while slow conversion and poor yields were observed for PBr_3, PBr_5 or $POBr_3$[19] (entries 3–5). It's worth mentioning that lots of reduced products, quinoline, was detected for PBr_3 and PBr_5 additives, indicating that they are good reducing agents for *N*-oxides. Utilizing Vilsmeier reagent bromide analogue, which was generated in situ by $POBr_3$ and DMF, we were pleased to observe the formation of the desired product in 26% yield (entry 6), along with quinoline as the major product. In order to diminish those byproducts, we assessed reaction concentration (entries 6–8), DMF equivalents (entries 9–10) and solvent effect (entries 12–15). It's worth noting that this transformation was remarkably sensitive to both solvent and concentration. Both DCM (entry 7) and THF (entry 12) afford moderate yields, whereas only little conversion could be detected for acetonitrile or DMF, and even no reaction for ether. Another Vilsmeier reagent analogue, which was produced by $POBr_3$ and *N*-methylformanilide, was also tested. However, little reaction was detected for this case (entry 11). Ultimately, we determined that the original proposed Vilsmeier reagent bromide analogue offers the best result (48%, entry 7). The product was obtained in moderate yield, along with 4-bromoquinoline regioisomer (C2:C4=3.6:1) and little quinoline byproducts. Although two side-products were accompanied, the desired product could be easily separated by flash column chromatography.

As shown in Tables 2 and 3, the optimized reaction conditions were applied to a series of azine-*N*-oxides, and we were pleased to obtain a diverse array of 2-bromoazines in modest to high yields, and with excellent regioselectivity for most cases. It's interesting to note that all reactions of isoquinoline *N*-oxides and few reactions of quinoline *N*-oxides were slow, extra $POBr_3$ and DMF were required to ensure reaction completion, which is presumably due to the worse reactivity of isoquinoline *N*-oxides than that of quinoline *N*-oxides.[20] In general, those halogen-substituted azine-*N*-oxides performed most effectively in the transformation (such as **11b–d** and **14d**). In addition, no interconversion with the existing halogen was observed for those substrates. Interestingly, it seems that the electron density of azine-*N*-oxides doesn't influence the reactivity.

Table 1
Reaction optimization for the 2-chlorination of quinoline-*N*-oxides[a]



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Entry	Additive	Solvent	M	DMF/equiv	Yield [%]
1	BBr_3	DCM	0.1	0	n/r[b]
2	TMSBr	DCM	0.1	0	n/r
3	PBr_3	DCM	0.1	0	9[c]
4	PBr_5	DCM	0.1	0	<10[c]
5	$POBr_3$	DCM	0.1	0	15
6	$POBr_3$	DCM	0.2	0.5	26[c]
7	$POBr_3$	DCM	0.1	0.5	48
8	$POBr_3$	DCM	0.05	0.5	30
9	$POBr_3$	DCM	0.1	1.0	41
10	$POBr_3$	DCM	0.1	2.0	37
11	$POBr_3$	DCM	0.1	0.5[d]	<10
12	$POBr_3$	THF	0.1	0.5	40
13	$POBr_3$	Et_2O	0.1	0.5	n/r
14	$POBr_3$	CH_3CN	0.1	0.5	21
15	$POBr_3$	DMF	0.1	N/A	<10[c]

[a] Unless otherwise noted, all reactions were conducted with **8** (1.00 equiv), additive (1.20 equiv) at rt until no further reaction could be detected.
[b] No reaction.
[c] Lots of deoxygenation products were detected.
[d] Instead of DMF, this is the equiv of *N*-methylformanilide.