ORGANIC LETTERS

2013
Vol. 15, No. 4
792–795

Regioselective Bromination of Fused Heterocyclic *N*-Oxides

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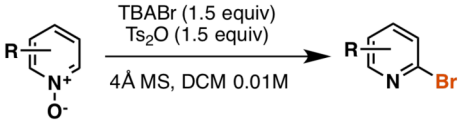
Received December 18, 2012

ABSTRACT

Mild, regioselective method for the 2-bromination of N-oxides



18 examples; yields up to 97%; single regioisomer in all cases

A mild method for the regioselective C2-bromination of fused azine *N*-oxides is presented, employing tosic anhydride as the activator and tetra-*n*-butylammonium bromide as the nucleophilic bromide source. The C2-brominated compounds are produced in moderate to excellent yields and with excellent regioselectivity in most cases. The potential extension of this method to other halogens, effecting C2-chlorination with Ts_2O/TBACl is also presented. Finally, this method could be incorporated into a viable one-pot oxidation/bromination process, using methyltrioxorhenium/urea hydropgen peroxide as the oxidant.

C2-substituted heteroarenes are common motifs in bioactive molecules. The synthesis of these compounds commonly relies on C−C bond formation through cross-coupling reactions or the introduction of heteroatoms through S_NAr techniques, both requiring prior generation of the C2-halogenated derivative.[1] Unfortunately, direct incorporation of halogens onto heterocycles (Figure 1A, **1**→**3**) proves challenging, as issues of poor regioselectivity and over halogenation often arise. C2-halogenation via the corresponding *N*-oxides (readily available via oxidation of the parent arenes) provides a popular alternative strategy (Figure 1A). Thus, chlorination is commonly achieved using $POCl_3$ or PCl_5 whereas iodination often requires a metalation based strategy.[2,3] Comparatively, there is a dearth of mild, reliable methods for *N*-oxide bromination. There have been a few reports on the bromination of 7-azaindoles, at both the 2- and 4-position,[4] but these reported methods have not found wide application, most likely due to lack of generality. By far the most common methods use $POBr_3$ or Br_2 at elevated temperatures.

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10.1021/ol3034675
Published on Web 01/25/2013

However, regiocontrol is largely substrate dependent and des-bromo product, as well as over bromination, are normally observed as major side reations; in addition, exposure of *N*-oxides to prolonged heating can cause safety concerns regarding thermal stability and the liability of exothermic degradation.

The lack of mild, reliable, and scalable methods for *N*-oxide bromination came to our attention during recent efforts to prepare kilogram quantities of a drug candidate. In this letter, the invention of a simple and scalable method for the synthesis of C2-bromo fused azines, from the corresponding *N*-oxide precursors, is described. This new method proves applicable to both electron-deficient and electron-rich heterocycles, including quinolines, isoquinolines, and azaindoles, possessing a variety of substitution patterns. The potential extension of this method to chlorinations is also demonstrated as well as a one-pot oxidation/bromination sequence that obviates the need for isolation of the *N*-oxide intermediates.

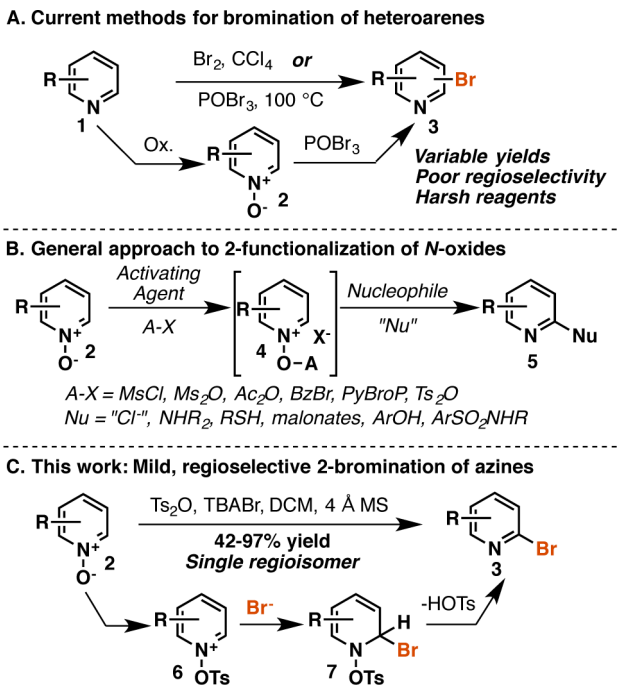
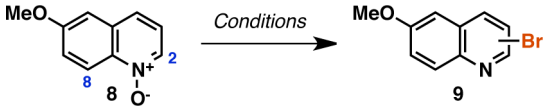


Figure 1. (A) Common methods for heteroarene and *N*-oxide bromination. (B) Functionalization of *N*-oxides via activating agent/nucleophile. (C) Novel method for mild, regioselective bromination.

The design of a new method built upon promising precedents is summarized in Figure 1B. In such a method, coordination of an activating agent to the *N*-oxide would enhance the electrophilic character of the C2-position, followed by attack of a bromide ion and subsequent deprotonation/aromitization to give the C2-substituted products, similar to a Reissert–Henze reaction (Figure 1C).[5] This approach is widely used in the context of *N*-oxides[6] and has been used for chlorination;[7] however issues of regioselectivity, observation of des-oxygenation, and, in many cases, competing addition of the activator counterion are problematic. Two recent encouraging reports in the literature, by Wei[6a] and Yin,[6b] showed that a range of heteroatom nucleophiles were added selectively at the C2-position when PyBroP (PyBroP = Bromotripyrrolidinophosphonium hexafluorophosphate) or Ts_2O was used as the activating agent. By adopting a similar approach but substituting the nucleophile with an appropriate bromide source, we hoped to obtain the C2-brominated compounds while avoiding the aforementioned competing side reactions (Figure 1C).

Using commercially available 6-methoxyquinoline *N*-oxide (**8**), a variety of activating agent/bromide combinations were screened for selective C2-bromination (Table 1). As expected, when standard bromination conditions, such as $POBr_3$, were utilized (Table 1, entries 1–6) multiple competing processes occurred. However, two new alternative conditions were identified, enabling the desired C2-bromination with much improved efficiency and selectivity (Table 1, entries 7 and 10). We were pleased to discover that PyBroP can function as both the activating agent and the external bromide source, delivering the C2-bromide in 69% isolated yield, with 5:1 regioselectivity. It was hypothesized that the regioselectivity arose from prior coordination to the *N*-oxide and delivery of the bromide intramolecularly through a pentavalent phosphorus intermediate. Alternatively, the use of Ms_2O/TBABr gave both a significantly higher yield and regioselectivity (Table 1, entry 8) while maintaining the mild reaction conditions. We then investigated the use of other sulfonyl anhydrides, and while Tf_2O gave no desired product, the use of Ts_2O

Table 1. Screening of Activator/Bromine Source Combinations



entry	conditions	C2:C8	conversion
1	PPh_3, Br_2	1:1.03	22
2	PPh_3, NBS	2.2:1	17
3	$POBr_3$	n.d.	<1
4	$SOBr_2$	n.d.	<1
5	oxalic bromide	n.d.	<1
6	acetyl bromide	n.d.	<1
7	PyBroP, 4 A MS, CF_3Ph, K_3PO_4	5:1	84 (69)[a]
8	Ms_2O, TBABr, THF, 4 A MS[b]	15:1	90
9	Tf_2O, TBABr, THF, 4 A MS[b]	n.d.	<1
10	**Ts_2O, TBABr, THF, 4 A MS**[b]	**15:1**	**100 (97)**[a]

[a] Isolated yield. [b] TBABr and substrate stirred with molecular sieves 10 min prior to addition of activator.

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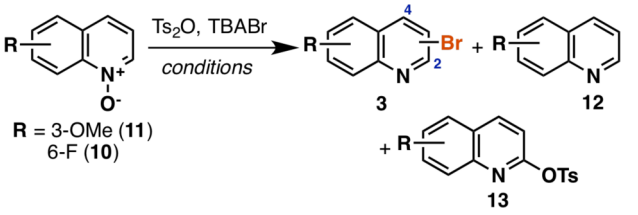
Table 2. Optimization of Reaction Conditions with **10** and **11**



entry	compd	solvent	[M]	conv	*3*	**12**	**13**
1	**11**	THF	0.1	100	82 [1:1][a]	18	0
2	**11**	CPME	0.1	95	100	0	0
3	**11**	Et_2O	0.1	80	100	0	0
4	**11**	CF_3Ph	0.1	100	100	0	0
5	**11**	PhMe	0.1	100	100	0	0
6	**11**	**DCM**	**0.1**	**100**	**100**	**0**	**0**
7	**10**	DCM	0.1	100	0	0	100
8	**10**	**DCM**	**0.01**	**100 (71)[b]**	**100**	**0**	**0**
9	**8**	**DCM**	**0.01**	**100 (97)[b]**	**100[c] [>30:1]**	**0**	**0**

[a] [1:1] C2:C4 regioisomers. [b] Isolated yield. [c] Only single regioisomer detected by ^{1}H NMR.

gave further improvement (Table 1, entry 10), affording the product with both the highest yield (97%) and regioselectivity (15:1); as such these conditions were chosen for further exploration.

Unfortunately, when this same reagent system was applied in the context of 6-fluoroquinoline *N*-oxide (**10**) and 3-methoxyquinoline *N*-oxide (**11**), significant formation of byproducts was observed, including regioisomers (**3**), des-bromo product (**12**), and a C2-*O*-tosyl derivative (**13**) (Table 2, entries 1 and 7).

In order to address these issues, a range of solvents and reaction concentrations were examined (Table 2). In the case of **11**, we hypothesized reduction product **12** to be a result of hydride donation from THF, and indeed **12** was not observed in any other solvent in our screen (Table 2, entries 2–6). Interestingly, the use of DCM not only eliminated reduction but also gave exclusive formation of the C2 isomer (as determined by ^{1}H NMR). Turning our attention to 6-fluoroquinoline (**10**), it was hypothesized that **13** was forming as a result of a dimerization reaction, since molecular sieves were present to eliminate water. Alternatively, attack of a second *N*-oxide to the 2-position of an activated species would lead to generation of the amide after deoxygenation. Tosylation of the resulting amide under the reaction conditions would then give **13**. To circumvent this issue, we first attempted slow inverse addition of the *N*-oxide; however this was unsuccessful. Gratifyingly, running the reaction at lower concentration (0.01 M in DCM) led to 71% isolated yield of the desired compound with none of the undesired byproduct observed. When these optimized conditions were applied in the context of the first model substrate, 6-methoxyquinoline *N*-oxide (**8**), we saw no loss in conversion and now obtained a *single regioisomer* (Table 2, entry 9). Using these optimized

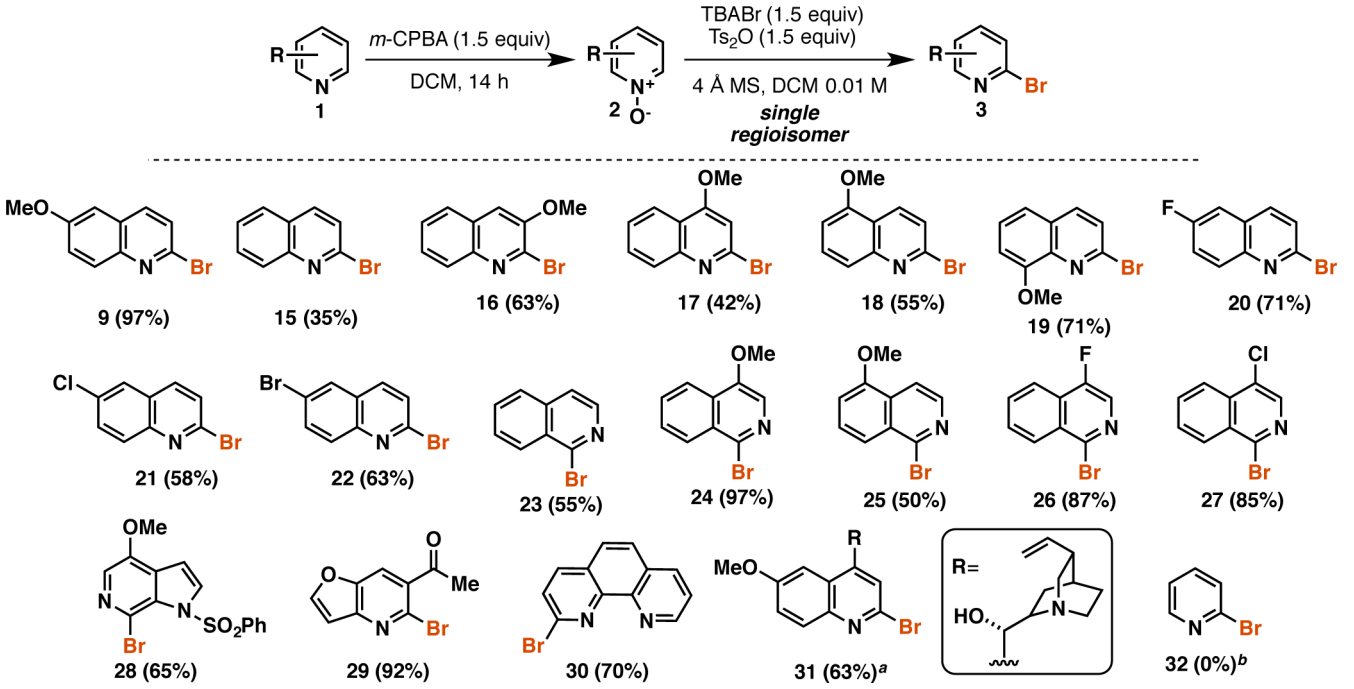


Figure 2. Scope of *N*-oxide bromination. All compounds were obtained as a single regioisomer. [a]Reaction run with 2.5 equiv of Ts_2O and 4 equiv of TBABr. [b]For a comprehensive list of simple pyridine derivatives examined, see Supporting Information.

conditions, the rate of the reaction was examined with both **8** and **10**, and it was found that the reaction was complete within 30 min in both cases.

With improved conditions in hand the scope of the bromination was examined (Figure 2). A range of quinoline and isoquinoline derivatives were brominated in modest to high yields and with excellent regioselectivity for the isomers shown. Particularly compelling is the bromination of the antimalarial agent quinine (**31**), which proceeded in high yield despite the presence of an olefin, tertiary alcohol, and tertiary amine. Both electron-rich and -poor substrates reacted well; furthermore, in the case of halo-substituted derivatives (**20**, **21**, **26**, and **27**) no interconversion with the existing halogen was observed. This methodology also proved applicable to azaindole **28** as well as fused pyridine derivative **29**, which possesses a sensitive acyl moiety. Another attractive feature of this method is scalability: the bromination of **8** was performed on a gram scale with no loss of regioselectivity and in 75% isolated yield (see Supporting Information for details). However, to date and despite our best efforts, the extension of Ts_2O/TBABr to the bromination of simple substituted pyridines has not been successful and is the subject of ongoing investigation (Figure 2, **32**).

We recognized the potential extension of this method to the introduction of other halogens simply by switching the tetrabutylammonium salt. Again using **8** as our model substrate, we found TBACl to be very effective, giving the 2-chloro product (**14**) in 96% yield, with 10:1 regioselectivity (Figure 3A).

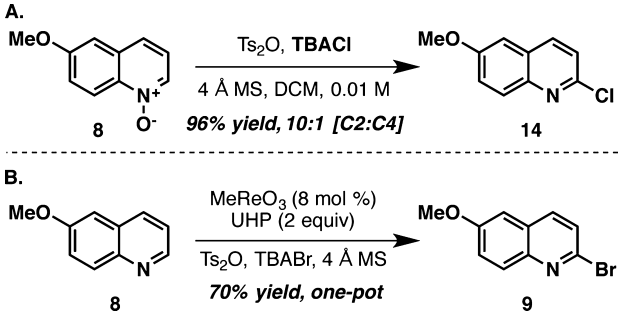


Figure 3. (A) Analogous chlorination of **8**. (B) One-pot oxidation/bromination sequence.

Finally, performing both the oxidation and bromination in a one-pot process was explored, thus eliminating the need for prior oxidation and isolation of the *N*-oxide, thus affecting the equivalent of a direct C−H bromination (Figure 3B). A range of oxidation conditions were screened using 6-methoxyquinoline (**8**), and it was found that the use of MTO/UHP,[8] followed by the addition of molecular sieves, TBABr, and Ts_2O gave the desired brominated compound in 70% yield in a one-pot fashion.[9]

In conclusion, a simple method for the regioselective bromination of a range of fused heterocyclic *N*-oxides has been developed. The method employs Ts_2O as the activiating agent and TBABr as the nucleophilic bromide source. The procedure has been conducted on a gram scale, is applicable to complex molecules (as demonstrated by the successful bromination of quinine), and has been extended to the incorporation of chlorine using TBACl. Finally, a viable one-pot oxidation/bromination procedure was developed employing MTO/UHP as the oxidant. The use of this activation method in other contexts such as iodination, fluorination, and other functionalizations are clear areas for additional study.

Acknowledgment. We would like to thank the Deutsche Forschungsgemeinschaft for a postdoctoral fellowship (WE 5022/1-1) for A.W. This work was supported by a collaboration between Bristol-Myers Squibb Company and The Scripps Research Institute.

Supporting Information Available. Experimental procedures, copies of all spectral data, and full characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) The bromination conditions are tolerant of up to 5 wt % of the rhenium catalyst.

The authors declare no competing financial interest.