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Metal-Free Amidation of Ethers with *N*,*N*-Dibromosulfonamides

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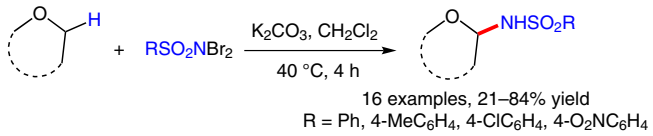

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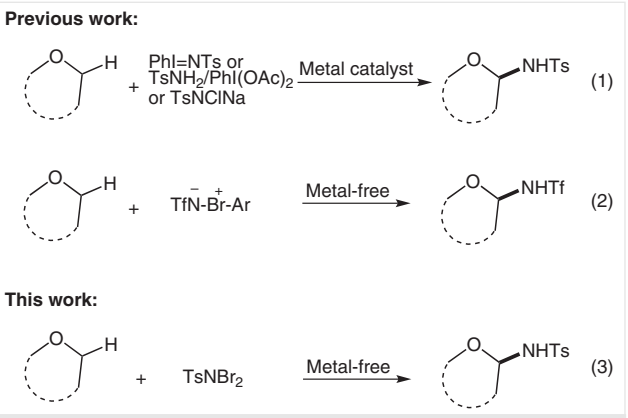
Abstract A new metal-free amidation of ethers with *N*,*N*-dibromosulfonamides has been developed. A series of hemiaminal ethers or imines were prepared with moderate to good yields.

Key words amidation, amides, *N*,*N*-dibromosulfonamides, ethers, hemiaminal ethers, nitrene, regioselectivity

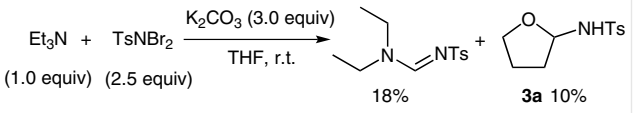
The regioselective construction of C–N bonds is considered to be an important approach due to the ubiquitous presence of amines in many biologically active natural products and pharmaceutical compounds.[1] Therefore, many remarkable endeavors have been made to develop efficient and general methods for the amination reactions.[2] Amidation of ethers by transition-metal-catalyzed nitrene insertion into C–H bonds has been shown to be the most efficient and synthetic useful method for the construction of hemiaminal ether frameworks.[3,4] For example, Che and coworkers developed amidation of THF with PhI=NTs or $TsNH_2$/$PhI(OAc)_2$ catalyzed by ruthenium and manganese porphyrins (Scheme 1, eq. 1).[5] Díaz-Requejo, Pérez, and coworkers developed copper–homoscorpionate complex catalyzed amidation of cyclic ethers by using PhI=NTs or TsNClNa (chloramine-T) as a nitrene source.[6] Then Yu and coworkers developed simple copper salt [$Cu(OTf)_2$] catalyzed amidation of cyclic ethers by using PhI=NTs or $TsNH_2$/$PhI(OAc)_2$ as a nitrene source.[7] On the other hand, photoinduced radical strategy and oxidative cross-dehydrogenative-coupling strategy have also been developed for the amination of ethers.[8,9] Notably, metal-free amidation of cyclic ethers by nitrene insertion have been reported by Ochiai and coworkers, in which hypervalent *N*-triflylimino-λ³-bromane was used as a nitrene source to realize amidation of ethers under transition-metal-free conditions (Scheme 1, eq. 2).[10] Yet, despite Ochiai's environmentally benign method using the active organonitrenoid specie, the metal-free amidation of ethers by nitrene-insertion strategy is sparse in the literature. Here we wish to report a metal-free amidation of ethers by using readily available *N*,*N*-dibromosulfonamides as nitrene sources under mild conditions (Scheme 1, eq. 3).



Scheme 1 Amidation of ethers

During the course of our studies on the bromoform reaction of tertiary amines with *N*,*N*-dibromo-4-methylbenzenesulfonamide ($TsNBr_2$) in THF, we noticed that small amounts of α-(*N*-tosylamino)tetrahydrofuran (**3a**) were formed when $TsNBr_2$ was employed (Scheme 2).[11] As active reagents, *N*,*N*-dibromosulfonamides can be used as bromine sources, as amine sources, as sources of both amine and bromine, or as others.[12] However, amidation of ethers using *N*,*N*-dibromosulfonamides under metal-free conditions has never previously been reported. Additionally, hemiaminal ether group is generally presented in many

natural products and some biologically active pharmaceutical compounds.[13] Then we decided to study this metal-free amidation reaction on both of the mechanism and its scope.



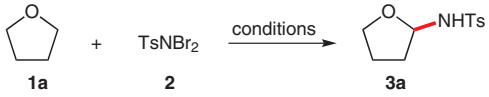
Scheme 2 Bromoform reaction of triethylamine (Et_3N) with $TsNBr_2$ in THF

The results of the optimization studies are summarized in Table 1. Simply mixing $TsNBr_2$ and K_2CO_3 in THF at room temperature for four hours gave **3a** in 9% yield (Table 1, entry 1), indicating that Et_3N is unrelated to this reaction. Decreasing the amount of THF from 120 to 10 equiv afforded a 26% yield of the amidation product **3a** (Table 1, entry 2). To our delight, stoichiometric amount of THF resulted in a comparable yield of **3a** (Table 1, entry 4 vs. entry 2). Screening of solvents was carried out with a mixture of THF and $TsNBr_2$ in a ratio of 1:1 in the presence of 3.0 equivalents of K_2CO_3 (Table 1, entries 4–6), and we found that CH_2Cl_2 is a suitable solvent. Other bases such as Na_2CO_3, $NaHCO_3$, NaOAc, NaOH, and KOH were also screened, however, no further improvement was achieved (Table 1, entries 7–12). Next, changing the ratio of the reactants resulted in significant difference in the reaction yields. When the reaction was carried out in a ratio of 1:1.5 (THF/$TsNBr_2$) in the presence of 5.0 equivalents of K_2CO_3, the desired product **3a** was obtained in 44% yield (Table 1, entry 13). Satisfactorily, a dramatic increase in yield was detected when the reaction temperature was raised to 40 °C (Table 1, entry 14). Further increasing the reaction temperature in 1,2-dichloroethane (DCE) diminished the reaction (Table 1, entry 20). Notably, replacement of $TsNBr_2$ with chloramine-T gave no desired amidation product (Table 1, entry 21).[14]

With the optimized reaction conditions in hand,[15] the substrate scope of this metal-free amidation reaction was explored. The results are summarized in Table 2. Both tetrahydropyran (**1b**) and 1,4-dioxane (**1c**) resulted in the desired α-amidation products with good yields when excess cyclic ethers were used (Table 2, entries 2, 3). Isochroman (**1d**) bearing two different α-methylene groups gave only the benzylic α-amidation product **3d** in 88% yield under the optimized conditions (Table 2, entry 4). Notably, nitrene insertion into benzylic C–H bonds has been reported previously,[12] here the sole regioselectivity was achieved, indicating the position is more active for the nitrene insertion. Oxepane was also suitable substrate for this amidation reaction, and the desired hemiaminal **3e** was obtained in 53% yield (Table 2, entry 5).

Interestingly, treatment of morpholine under the optimized conditions gave no desired product, but diaziridine **3f** was obtained in 71% yield (Table 2, entry 6).[15] Acyclic

Table 1 Amidation of THF with $TsNBr_2$[a]



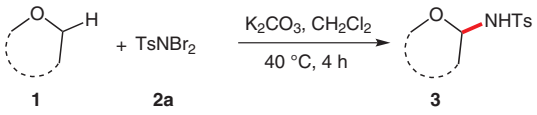
Entry	1a/2	Base (equiv)[b]	Temp (°C)	Solvent	Yield (%)[c]
1	120:1	K_2CO_3 (3.0)	r.t.	THF	9
2	10:1	K_2CO_3 (3.0)	r.t.	CH_2Cl_2	26
3	5:1	K_2CO_3 (3.0)	r.t.	CH_2Cl_2	25
4	1:1	K_2CO_3 (3.0)	r.t.	CH_2Cl_2	24
5	1:1	K_2CO_3 (3.0)	r.t.	MeCN	6
6	1:1	K_2CO_3 (3.0)	r.t.	EtOAc	3
7	1:1	Na_2CO_3 (3.0)	r.t.	CH_2Cl_2	7
8	1:1	NaOAc (3.0)	r.t.	CH_2Cl_2	8
9	1:1	$NaHCO_3$ (3.0)	r.t.	CH_2Cl_2	trace
10	1:1	NaOH (3.0)	r.t.	CH_2Cl_2	trace
11	1:1	KOH (3.0)	r.t.	CH_2Cl_2	trace
12	1:1.2	K_2CO_3 (3.0)	r.t.	CH_2Cl_2	28
13	1:1.5	K_2CO_3 (5.0)	r.t.	CH_2Cl_2	44
14	1:1.5	K_2CO_3 (5.0)	40	CH_2Cl_2	84
15	1:1.5	Cs_2CO_3 (5.0)	40	CH_2Cl_2	trace
16	1:1.5	KO*t*-Bu	40	CH_2Cl_2	trace
17	1:1.5	Na_3PO_4 (5.0)	40	CH_2Cl_2	61
18	1:1.5	DBU (5.0)	40	CH_2Cl_2	–
19[d]	1:1.5	K_2CO_3 (5.0)	40	CH_2Cl_2	62
20	1:1.5	K_2CO_3 (5.0)	80	DCE	27
21[e]	1:1.5	K_2CO_3 (5.0)	40	CH_2Cl_2	–

[a] Reactions were carried out with **1a** (0.2 mmol for entries 4–21), $TsNBr_2$ (0.2 mmol for entries 1–3), base in solvent (2.0 mL) for 4 h.
[b] Conditions: Based on 1.0 equiv of **1a** (entries 4–21) or **2** (entries 1–3).
[c] Isolated yield.
[d] Conditions: 0.02 mmol NaI was used.
[e] Replaced $TsNBr_2$ with chloramine-T.

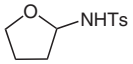
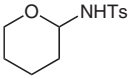
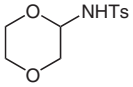
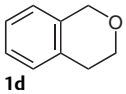
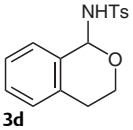
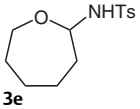
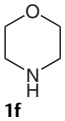
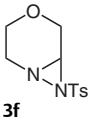
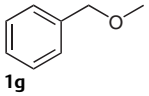
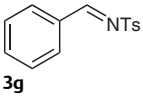
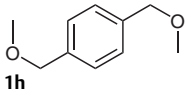
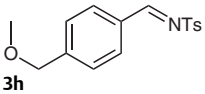
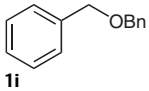
ether such as diethyl ether, methyl *tert*-butyl ether did not result in the desired amidation product. However, acyclic benzyl ethers were shown to be suitable substrates for this metal-free amidation reaction. In these cases, the hemiaminal ethers products could not be isolated, but the imine compounds were obtained (Table 2, entries 6–8), a result of elimination of an alcohol. This phenomenon has been observed previously.[7b,10b] Finally, performing the reaction on a large scale showed no change in efficiency (Table 2, entry 1).

Besides $TsNBr_2$, other *N*,*N*-dibromosulfonamides are also suitable for this reaction. *N*,*N*-Dibromobenzenesulfonamide, *N*,*N*-dibromo-4-chloro-benzenesulfonamide, and *N*,*N*-dibromo-4-nitrobenzenesulfonamide all returned the desired hemiaminal ethers in 55%, 56%, and 27% yields, respectively (Table 3, entries 2–4). It seemed that a strong electron-withdrawing group on the benzene ring of *N*,*N*-di-

Table 2 Amidation of Ethers Using $TsNBr_2$[a]



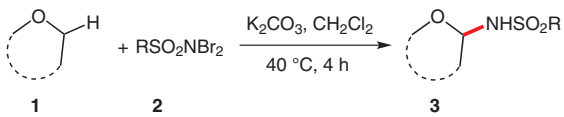
1 2a 3

Entry	Substrate	Product	Yield (%)[b]
1	 **1a**	 **3a**	83 (84)[c]
2[d]	 **1b**	 **3b**	76
3[d]	 **1c**	 **3c**	72
4	 **1d**	 **3d**	88
5	 **1e**	 **3e**	53
6	 **1f**	 **3f**	71
7	 **1g**	 **3g**	66
8	 **1h**	 **3h**	63
9	 **1i**	**3g**	87

[a] Reactions were carried out with **1a–g** (0.2 mmol), $TsNBr_2$ (0.3 mmol), K_2CO_3 (1.0 mmol) in CH_2Cl_2 (2.0 mL) at 40 °C for 4 h.
[b] Isolated yield.
[c] The reaction was conducted on a 10.0 mmol scale.
[d] The ratio of **1**/**2a**/K_2CO_3 is 8:1:5.

bromosulfonamide is harmful to the reaction yield (Table 3, entry 1 vs. entry 4), the reason may be ascribed to the decreased nucleophilicity of the corresponding nitrene intermediate. Reaction of *N*,*N*-dibromo-4-chlorobenzenesulfonamide with **1b**, **1c**, **1d**, and **1e** all gave the desired products with moderate to good yields (Table 3, entries 5–8).

Table 3 Amidation of Ethers Using *N*,*N*-Dibromosulfonamides[a]

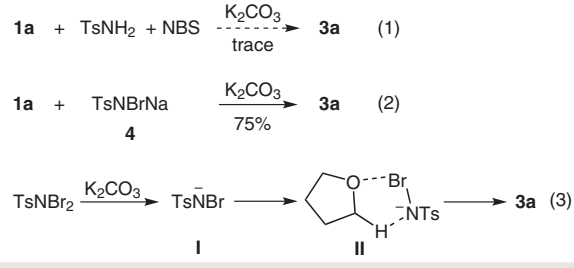


1 2 3

Entry	Substrate	R	Product	Yield (%)[b]
1	**1a**	4-MeC_6H_4	**3a**	84
2	**1a**	Ph	**3ab**	55
3	**1a**	4-ClC_6H_4	**3ac**	56
4	**1a**	4-$O_2NC_6H_4$	**3ad**	27
5	**1b**	4-ClC_6H_4	**3bb**	49
6	**1c**	4-ClC_6H_4	**3cb**	54
7	**1d**	4-ClC_6H_4	**3db**	82
8	**1e**	4-ClC_6H_4	**3eb**	21

[a] Reactions were carried out with **1** (0.2 mmol), RSO_2NBr_2 (0.3 mmol), K_2CO_3 (1.0 mmol) in CH_2Cl_2 (2.0 mL) at 40 °C for 4 h.
[b] Isolated yield.

To probe the mechanism, control experiments were conducted. Using $TsNH_2$ and NBS as reagents was found to be ineffective in offering any desired product (Scheme 3, eq. 1). However, replacing $TsNBr_2$ with TsNBrNa showed similar reactivity as the $TsNBr_2/K_2CO_3$ system (Scheme 3, eq. 2). These results demonstrated that the TsNBr ion maybe play an important role in this amidation reaction. A possible reaction pathway for this novel metal-free amidation reaction is depicted in Scheme 3 (eq. 3). Firstly, reaction of $TsNBr_2$ with K_2CO_3 leads to TsNBr ion intermediate (**I**), then reaction of **I** with THF gives an intermediate **II**, in which the electrophilic Br may interact with the Lewis basic oxygen, as a result of Lewis base activation of Lewis acid.[16] Thus the α-C–H bonds of THF are activated by the oxonium intermediate; meanwhile, the potential active nitrenoid specie is also activated, as the N–Br bond is more polarized. Furthermore, the intermolecular nitrene insertion reaction is transformed to an intramolecular reaction (generally intramolecular reactions are entropically favored).



Scheme 3 Control experiments and proposed reaction pathway

In summary, we have developed a new metal-free amidation of ethers with *N*,*N*-dibromosulfonamides. A series of hemiaminal ethers and imines were prepared with moder-

ate to good yields. Control experiments indicated that the TsNBr ion is responsible for this amidation reaction. Further investigations to better understand the mechanism and to develop new applications of this reaction are under way.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1561373.

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(14) For metal-catalyzed amination using chloramine-T as an amine source, see ref. 3 and 4.

(15) **4-Methyl-*N*-(tetrahydrofuran-2-yl)benzenesulfonamide (3a); Typical Procedure**

$TsNBr_2$ (**2**, 98.7 mg, 0.30 mmol) was added in one portion to a stirred solution of THF (**1a**, 16 µL, 0.20 mmol), and K_2CO_3 (137.9 mg, 1.0 mmol) in CH_2Cl_2 (2.0 mL). The mixture was stirred at 40 °C for 4 h, and the reaction mixture was cooled to room temperature. Then the reaction was quenched with sat. aq Na_2SO_3 (2.0 mL) and H_2O (2.0 mL). The mixture was extracted with CH_2Cl_2 (3 × 5.0 mL), and the extracts were combined, washed with brine (10.0 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, PE–EtOAc) to give **3a** as a white solid; yield 40.5 mg (84%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79 (d, *J* = 8.0 Hz, 2 H), 7.29 (d, *J* = 8.0 Hz, 2 H), 5.35 (ddd, *J* = 9.2, 6.4, 3.6 Hz, 1 H), 5.14 (d, *J* = 6.4 Hz, 1 H), 3.72–3.68 (m, 2 H), 2.42 (s, 3 H), 2.20–2.15 (m, 1 H), 1.91–1.75 (m, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.8, 138.4, 129.2, 126.6, 84.6, 66.7, 32.0, 23.6, 21.2. ESI-HRMS: *m/z* calcd for $C_{11}H_{15}NO_3SNa$ $[M + Na]^+$: 264.0665; found: 264.0672.

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