

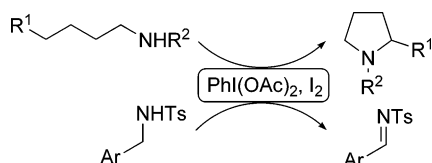
δ and α sp^3 C–H Bond Oxidation of Sulfonamides with $\text{PhI}(\text{OAc})_2/\text{I}_2$ under Metal-Free Conditions

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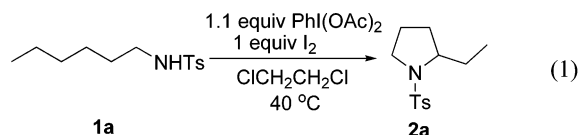
An efficient δ and α sp^3 C–H bond oxidation of sulfonamides with $\text{PhI}(\text{OAc})_2/\text{I}_2$ under metal-free conditions has been reported. The reaction provides a useful route to pyrrolidines, *N*-sulfonylimines, and various sulfonamide derivatives. The potential of this reaction system can be evaluated by its mild condition and simple process.

Unactivated sp^3 C–H bond oxidation and subsequent functionalizations have attracted considerable interest in past decades.¹ The cleavage of an unactivated sp^3 C–H bond has proven difficult because it is kinetically and thermodynamically unfavorable. Various transition-metal complexes have been used in the oxidation of sp^3 C–H bonds, and many excellent results in this area have been reported in recent years.² The oxidation of sp^3 C–H bonds, especially under metal-free conditions, however, remains challenging because of a lack of universal

applicability in this synthetic module. We herein present an efficient δ and α sp^3 C–H bond oxidation of sulfonamides for the synthesis of pyrrolidines and *N*-sulfonylimines with iodo-benzene diacetate ($\text{PhI}(\text{OAc})_2$) and iodine (I_2) under metal-free conditions.

Amination of saturated C–H bonds provides a great potential for the synthesis of amine derivatives.³ Intramolecular C–H bond amination attracted more attention owing to its efficiency and selectivity and to the synthetic significance of the heterocycles.⁴ In most cases, a transition-metal catalyst is present to promote the reaction. $\text{PhI}(\text{OAc})_2$ has been used as an oxidizing reagent in the Rh- or Ru-catalyzed C–H amination for the synthesis of five- or six-membered ring heterocycles. In these procedures, a primary amide is oxidized with $\text{PhI}(\text{OAc})_2$ to an iodimine, which is in turn decomposed by a metal complex to generate the corresponding metallonitrene. The following cyclization occurs via C–H insertion to give the heterocycle as product. Despite the great advantages of these approaches, there are still certain limitations: (1) the secondary amides, which cannot be oxidized to the corresponding iodimines, cannot take place under the same conditions; (2) a transition-metal complex is essential as catalyst in the reaction although it may cause other concerns.

As part of our program to develop the synthetic application of sulfonamides,⁵ we found a δ -C–H insertion amination of secondary amide, *N*-hexyl-4-methylbenzenesulfonamide **1a**, with $\text{PhI}(\text{OAc})_2$ and I_2 under metal-free conditions (eq 1). The reaction gave rise to a five-membered ring product, 2-ethyl-1-tosylpyrrolidine **2a**, in 12% yield. Control experiments indicated that $\text{Rh}_2(\text{OAc})_4$ could not catalyze the reaction. No cyclization product **2a** was formed in the absence of either $\text{PhI}(\text{OAc})_2$ or I_2 .



Subsequent investigations revealed that the desirable product **2a** could be isolated in 63% yield when 3 equiv of $\text{PhI}(\text{OAc})_2$ was used (Table 1). A further increase of the amount of $\text{PhI}(\text{OAc})_2$ did not result in the improvement of yield. A 0.5 equiv amount of I_2 was not enough to complete the reaction. The reaction was sensitive to the reaction temperature. While a best yield (82%) was obtained at room temperature, a drastic decrease

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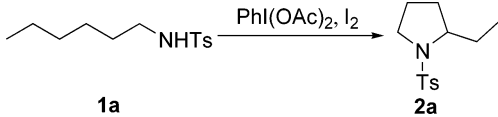
(1) For selected reviews, see: (a) Bergman, R. G. *Nature* **2007**, *446*, 391. (b) Tobisu, M.; Chatani, N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1683. (c) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921. (d) Davies, H. M. L.; Beckwith, R. E. *J. Chem. Rev.* **2003**, *103*, 2861. (e) Rittleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731. (f) Labinger, J. A.; Bercaw, J. E. *Nature* **2002**, *417*, 507. (g) Chen, H. Y.; Schlecht, S.; Semple, T. C.; Hartwig, J. F. *Science* **2000**, *287*, 1995. (h) Shilov, A. E.; Shul'pin, G. B. *Chem. Rev.* **1997**, *97*, 2879. (i) Arndtsen, B. A.; Bergman, R. G.; Mobley, T. A.; Peterson, T. H. *Acc. Chem. Res.* **1995**, *28*, 154.

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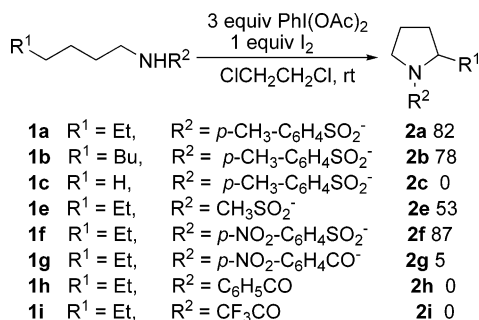
(4) For selected examples, see: (a) Liang, C.; Robert-Peillard, F.; Fruit, C.; Müller, P.; Dodd, R. H.; Dauban, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 4641. (b) Lebel, H.; Huard, K.; Lectard, S. *J. Am. Chem. Soc.* **2005**, *127*, 14198. (c) Williams Fiori, K.; Fleming, J. J.; Du Bois, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 4349. (d) Cui, Y.; He, C. *Angew. Chem., Int. Ed.* **2004**, *43*, 4210. (e) Fleming, J. J.; Williams Fiori, K.; Du Bois, J. *J. Am. Chem. Soc.* **2003**, *125*, 2028. (f) Hinman, A.; Du Bois, J. *J. Am. Chem. Soc.* **2003**, *125*, 11510. (g) Davies, H. M. L.; Venkataramani, C. *Org. Lett.* **2003**, *5*, 1403. (h) Liang, J. L.; Yuan, S. X.; Huang, J. S.; Yu, W. Y.; Che, C. M. *Angew. Chem., Int. Ed.* **2002**, *41*, 3465.

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TABLE 1. Condition Screening Experiments for Intramolecular Amination of *N*-Hexyl-4-methylbenzenesulfonamide^a


entry	oxidation (equiv)	solvent	T (°C)	yield ^b (%)
1	PhI(OAc) ₂ (2)/I ₂ (1)	ClCH ₂ CH ₂ Cl	40	42
2	PhI(OAc) ₂ (3)/I ₂ (1)	ClCH ₂ CH ₂ Cl	40	63
3	PhI(OAc) ₂ (4)/I ₂ (1)	ClCH ₂ CH ₂ Cl	40	64
4	PhI(OAc) ₂ (3)/I ₂ (0.5)	ClCH ₂ CH ₂ Cl	40	42
5	PhI(OAc) ₂ (3)/I ₂ (1)	ClCH ₂ CH ₂ Cl	reflux	7
6	PhI(OAc) ₂ (3)/I ₂ (1)	ClCH ₂ CH ₂ Cl	25	82
7	PhI(OAc) ₂ (3)/I ₂ (1)	ClCH ₂ CH ₂ Cl	0	4
8	PhI(OAc) ₂ (3)/I ₂ (1)	THF	25	nd ^c
9	PhI(OAc) ₂ (3)/I ₂ (1)	DMF	25	nd ^c
10	PhI(OAc) ₂ (3)/I ₂ (1)	<i>t</i> -BuOH	25	nd ^c
11	PhI(OAc) ₂ (3)/I ₂ (1)	toluene	25	nd ^c
12	PhI(OAc) ₂ (3)/I ₂ (1)	AcOEt	25	78
13	PhI(OAc) ₂ (3)/I ₂ (1)	CH ₂ Cl ₂	25	42

^a All reactions were conducted on a 0.5 mmol scale. ^b Isolated yield. ^c No product was detected.

SCHEME 1. Intramolecular C–H Bond Amination of Amides

in yield occurred when the reaction was warmed to reflux or cooled to 0 °C. No product was detected when THF, DMF, *t*-BuOH, or toluene was used as solvent, while the reaction could proceed in AcOEt and CH₂Cl₂ with varied efficiency. Shono reported the same conversion from **1a** to **2a** via an electrochemical oxidation, but the yield was only 22%.⁶

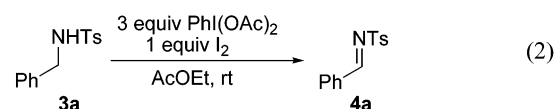
The reaction of *N*-octyl-4-methylbenzenesulfonamide **1b** proceeded smoothly and only gave expected five-membered ring products in good yields.⁷ However, *N*-butyl-4-methylbenzenesulfonamide **1c** did not react under the same conditions. A strong electron-withdrawing group on nitrogen was essential for the intramolecular amination. Sulfonamides **1e** and **1f** could be converted into the corresponding pyrrolidines. By contrast, benzamide **1h** and trifluoroacetamide **1i** were inactive in the cyclization (Scheme 1).

For the reaction of *N*-propyl-4-methylbenzenesulfonamide, the starting material disappeared, but no cyclization product was isolated. Analysis of the unpurified reaction mixture by ¹H NMR spectroscopy indicated the formation of TsNH₂ and propionaldehyde, generated as the decomposition products of corresponding sulfonimine.

The oxidation of a C–H bond α to nitrogen in secondary amines is employed to synthesize imines from amines. Although

many oxidation procedures have been developed,⁸ certain drawbacks of the approach, such as the requirement of an additional metal catalyst or other additives, and low solubility of oxidizer in organic solvent, limit the synthetic application of such processes. *N*-Sulfonylimines are one of the few types of stable electron-deficient imines and are of increasing importance because they are versatile intermediates in organic synthesis. Although there are a variety of methods developed for the preparation of *N*-sulfonylimines,⁹ the direct oxidation of sulfonamides to *N*-sulfonylimines remains an attractive option.

The oxidation of *N*-benzyl-4-methylbenzenesulfonamide **3a** gave rise to *N*-sulfonylimines **4a** 76% yield when AcOEt was used as solvent (eq 2). Guo have used Pd(OAc)₂ as catalyst in the oxidation of **3a** to **4a** with O₂, but the yield was very low (16%).^{8a} Control experiments indicated that no reaction occurred in the absence of either PhI(OAc)₂ or I₂.



The aryl *N*-sulfonylimines formed in the oxidation reactions were ready to undergo various subsequent addition reactions without further purification. As shown in Table 2, entries 1–6, cross-dehydrogenative-coupling (CDC) reactions between sulfonamide and malonate proceeded smoothly via the oxidations of sulfonamides and the subsequent additions with malonate.¹⁰ In these procedures, the oxidation reaction and the nucleophilic addition reaction were conducted in one flask, and generated the corresponding CDC products in good yields. When allylzinc bromide (Table 2, entries 8–11), allyltrimethylsilane (Table 2, entry 12), diethyl phosphate (Table 2, entry 13), or dimethyl acetylenedicarboxylate (eq 3) was used as nucleophile in the subsequent addition reaction, a workup procedure for the oxidation reaction mixture was necessary owing to the sensitivity of nucleophilic reagent or catalyst to the oxidizer. The yields

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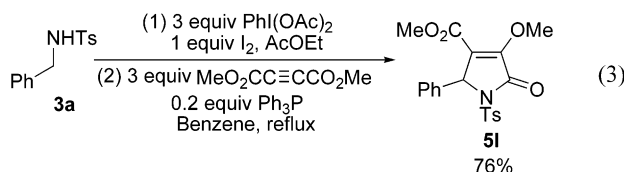
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TABLE 2. Oxidation Reactions of Sulfonamides and Subsequent Addition Reactions^a

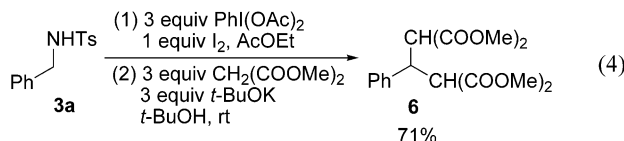
$\text{Ar}-\text{CH}_2-\text{NHTs} \xrightarrow[\text{(2) Nucleophile}]{\text{(1) 3 equiv PhI(OAc)}_2, \text{1 equiv I}_2, \text{AcOEt}} \text{Ar}-\text{CH}(\text{Nu})-\text{NHTs} \quad \mathbf{5}$			
entry	Ar	nucleophile (equiv) and conditions	5 ^b (%)
1 ^c	Ph	CH ₂ (COOEt) ₂ (2), <i>t</i> -BuOK (2), <i>t</i> -BuOH, rt	5a (82)
2 ^c	<i>p</i> -CH ₃ C ₆ H ₄	CH ₂ (COOEt) ₂ (2), <i>t</i> -BuOK (2), <i>t</i> -BuOH, rt	5b (78)
3 ^c	<i>p</i> -CH ₃ OC ₆ H ₄	CH ₂ (COOEt) ₂ (2), <i>t</i> -BuOK (2), <i>t</i> -BuOH, rt	5c (73)
4 ^c	<i>o</i> -ClC ₆ H ₄	CH ₂ (COOEt) ₂ (2), <i>t</i> -BuOK (2), <i>t</i> -BuOH, rt	5d (79)
5 ^c	<i>p</i> -FC ₆ H ₄	CH ₂ (COOEt) ₂ (2), <i>t</i> -BuOK (2), <i>t</i> -BuOH, rt	5e (83)
6 ^c	<i>o</i> -CF ₃ C ₆ H ₄	CH ₂ (COOEt) ₂ (2), <i>t</i> -BuOK (2), <i>t</i> -BuOH, rt	5f (81)
7 ^c	Ph	CH ₂ =CHCH ₂ ZnBr (3), THF, rt	5g (0)
8 ^d	Ph	CH ₂ =CHCH ₂ ZnBr (3), THF, rt	5g (84)
9 ^d	<i>p</i> -CH ₃ C ₆ H ₄	CH ₂ =CHCH ₂ ZnBr (3), THF, r.t.	5h (81)
10 ^d	<i>p</i> -CH ₃ OC ₆ H ₄	CH ₂ =CHCH ₂ ZnBr (3), THF, rt	5i (80)
11 ^d	<i>p</i> -FC ₆ H ₄	CH ₂ =CHCH ₂ ZnBr (3), THF, r.t.	5j (82)
12 ^d	Ph	CH ₂ =CHCH ₂ SiMe ₃ (3), Bu ₄ NF (0.1), THF, rt	5j (78)
13 ^d	Ph	HPO(OEt) ₂ (3), K ₂ CO ₃ (1), ClCH ₂ CH ₂ Cl, rt	5k (82)

^a Reactions were conducted on a 1 mmol scale. ^b Isolated yield. ^c After the oxidation reaction, nucleophilic reagent was added into directly. ^d The oxidation reaction was quenched with Me₂S (3 equiv), and after a workup with satd Na₂S₂O₃, the resulted concentrated crude product was treated with nucleophilic reagents under the corresponding conditions.

of these two-step reactions were not affected by the additional workup operation.

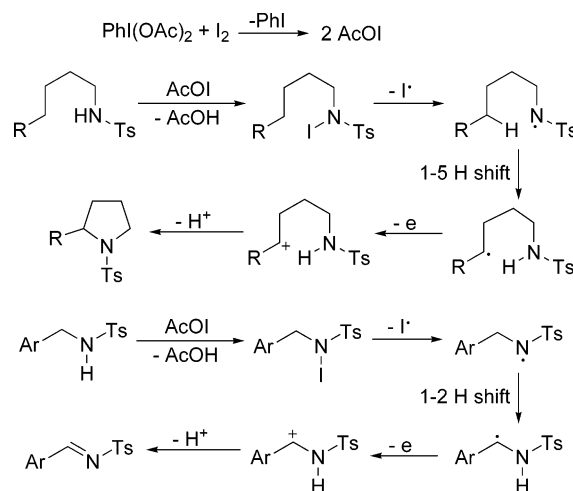
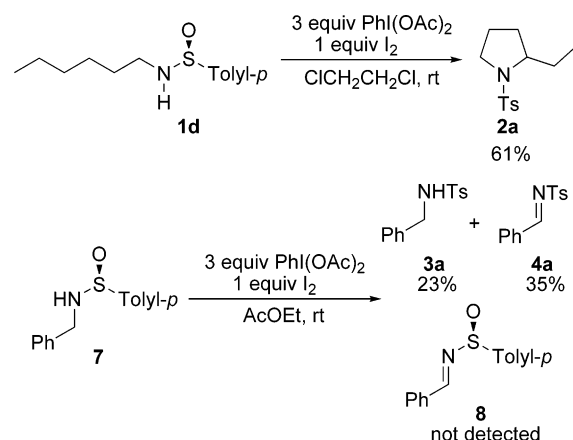


Further experiments showed that the oxidation and a tandem Knoevenagel–Michael addition of resulted *N*-sulfonylimine with diethyl malonate⁵ could be conducted in one flask (eq 4).



When (*S*)-*N*-hexyl-4-methylbenzenesulfonamide **1d** was used as the starting material, sulfonamide was oxidized to sulfonamide, and 2-ethyl-1-tosylpyrrolidine **2a** was formed as the final product. The oxidation of (*S*)-*N*-benzyl-4-methylbenzenesulfonamide **7** under the same conditions gave sulfonamide **3a** and *N*-sulfonylimines **4a** as the products, and no sulfinimine **8** was detected from the reaction (Scheme 2).

The PhI(OAc)₂/I₂ system has been used as a radical precursor to form sulfonamidyl radicals.¹¹ In these processes, however, photochemical treatments or ultrasonic irradiations were essential to promote the reactions. In our reaction conditions, extra *hν* or ultrasonic irradiation were not necessary. On the contrary, in the cases of formation of *N*-sulfonylimines, the utilization

**FIGURE 1.** Tentative mechanism for the δ and α sp³ C–H bond oxidation of sulfonamides with PhI(OAc)₂/I₂.**SCHEME 2. Oxidation of 4-Methylbenzenesulfonamides 1d and 7**

of *W* – *hν* or ultrasonic irradiation resulted in the decomposition of the formed *N*-sulfonylimines.

A tentative mechanism for the products formation is proposed in Figure 1. The reaction of PhI(OAc)₂ and iodine generated iodobenzene and acetyl hypoiodite. Sulfonamides then reacted with acetyl hypoiodite to form sulfonamidyl radicals.^{11d} In the cases of *N*-hexylsulfonamides, sulfonamidyl radicals underwent a 1, 5-H shift to form δ carbon radicals, which was a very easily oxidizable species. After an oxidation to carbocation and the subsequent cyclization, five-membered ring products were generated.¹² Sulfonamidyl radicals with benzyl groups were converted into α carbon radicals via a 1,2-H shift. Aryl sulfonylimines were obtained as the result of the following oxidation and deprotonation.^{8d}

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In summary, we report here an efficient δ and α sp^3 C–H bond oxidation of sulfonamides with $\text{PhI}(\text{OAc})_2/\text{I}_2$ under a metal-free condition. The reaction provides a useful route to pyrrolidines, *N*-sulfonylimines and various sulfonamide derivatives. The potential of this reaction system can be demonstrated by its mild condition and simple process. The reaction mechanism, scope, and synthetic application are ongoing and will be reported in due course.

Experimental Section

General Procedure for δ C–H Amination Cyclization of Sulfonamides. A Schlenk tube was charged with $\text{PhI}(\text{OAc})_2$ (483 mg, 1.5 mmol) and sulfonamide (0.5 mmol), evacuated, and backfilled with argon. I_2 (127 mg, 0.5 mmol) and DCE (2 mL) were successively added. Then the reaction mixture was stirred at room temperature until the sulfonamide disappeared monitored by TLC. The mixture was quenched with saturated $\text{Na}_2\text{S}_2\text{O}_3$ and extracted by ethyl acetate (100 mL $\times$ 3). The organic layer was

dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography on silica gel to provide the desired product. 2-Ethyl-1-tosylpyrrolidine **2a**: ^1H NMR (400 MHz, CDCl_3) δ 7.70 (d, J = 8.2 Hz, 2H), 7.29 (d, J = 8.2 Hz, 2H), 3.50–3.55 (m, 1H), 3.32–3.37 (m, 1H), 3.16–3.20 (m, 1H), 2.41 (s, 3H), 1.81–1.88 (m, 1H), 1.72–1.80 (m, 1H), 1.41–1.61 (m, 4H), 0.90 (t, J = 7.2 Hz, 3H). The spectral data are consistent with those reported in the literature.⁶

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Supporting Information Available: Experimental procedures, characterization data, and copies of ^1H and ^{13}C NMR of new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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