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Facile iodine(III)-induced oxidative cycloaddition of *N*-sulfonyl imines with methylene compounds under neutral conditions

Renhua Fan [a,*], Linfei Wang [a], Yang Ye [a], Jin Zhang [b]

[a] Department of Chemistry, Fudan University, 220 Handan Road, Shanghai 200433, China
[b] Pharmacy School, Shenyang Pharmaceutical University, 103 Wenhua Road, Shenyang, Liaoning 110016, China

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ABSTRACT

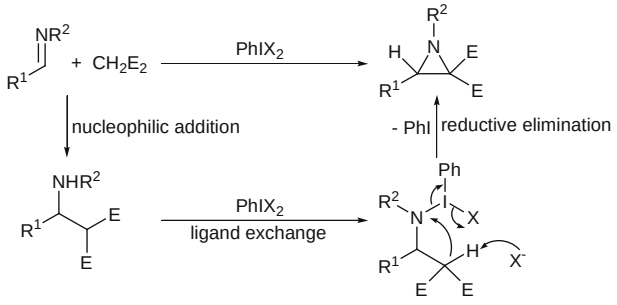
An efficient oxidative cycloaddition of *N*-sulfonyl imines with methylene compounds using PhIO with a catalytic amount of KI under neutral conditions, which affords 2,2-difunctionalized aziridines in good to excellent yields, is reported.

In past decades, the versatility of polyvalent iodine organic compounds has been well recognized, and attracted especially active interest.[1,2] Iodine(III) and iodine(V) derivatives are now used extensively in organic synthesis as a result of their benign environmental character and ready availability. Besides the very useful oxidizing properties, a notable feature of the organic iodine(III) compounds is their ability to undergo ligand exchange reaction and reductive elimination reaction like transition metals.[1–3] This feature allows construction of various carbon–carbon, hetero–heteroatom, and carbon–heteroatom bonds. The elegance of these stepwise tactics led us to investigate the possibility of direct cycloaddition of imines with methylene compounds induced by iodine(III) compounds (Scheme 1).[4] The resulting 2,2-difunctionalized aziridines have recently been identified as protease inhibitors, and potentially attractive starting materials for many biologically active substances.[5,6]

To verify our hypothesis, a set of experiments was carried out using *N*-Ts imine **1a** and diethyl malonate **2a** as model substrates. The preliminary survey, carried out in the presence of *t*-BuOK in CH_3CN at room temperature, allowed us to evaluate the efficiency of various iodine(III) compounds. Gratifyingly, we observed the formation of desired aziridine **3a** in the reaction with PhIO, albeit in a low yield (Table 1, entry 3). Diethyl 2-benzylidenemalonate was isolated as the major byproduct (in 41% yield). This byproduct was proposed to be generated from the Knoevenagel condensation of imine with malonate under the basic condition.[7]

Due to the polymeric structure of PhIO, a hydroxylic solvent or a catalyst is normally required to depolymerize $(PhIO)_n$ to generate the reactive species.[1,8] In our experiments, inferior results were displayed when a Lewis acid ($BF_3{\cdot}Et_2O$), or hydroxylic solvents (H_2O, MeOH, and *t*-BuOH) were used (Table 1, entries 4–7). Interestingly, the addition of 1 equiv of KI accelerated the reaction remarkably. The reaction was complete in 5 min and resulted in a higher isolated yield (Table 1, entry 8). Further investigation revealed that the yield was dramatically improved in the absence of *t*-BuOK, while no Knoevenagel condensation product was detected from the reaction (Table 1, entry 9). When 1 equiv of PhIO was used, reaction did not go to completion even after 1 h (Table 1, entry 10). Acetonitrile was the optimum solvent for the reaction (Table 1, entries 12–15). It was noteworthy that a catalytic amount of KI could efficiently promote the oxidative cycloaddition reaction: a satisfactory isolated yield (93% yield) was achieved when 0.2 equiv of KI was utilized (Table 1, entry 17). Salts other than iodide did not catalyze the reaction effectively (Table 1, entries 19–22). In the control experiments with $PhI(OAc)_2$ and $PhI(OCOCF_3)$ under the same condition, no aziridine was detected (Table 1, entries 23 and 24).

The scope of this reaction was then investigated under optimized conditions [CH_2E_2 (1.1 equiv), PhIO (2.0 equiv), KI (0.2 equiv), CH_3CN, 25 °C], and the results are summarized in Table 2. For most cases, aryl *N*-sulfonyl imines **1** reacted with activated methylene compounds **2** leading to the corresponding products **3** in good to excellent yields, while no aziridine was formed in the



Scheme 1. Iodine(III) induced oxidative cycloaddition of imine with methylene compound.

* Corresponding author. +86 21 6564 3462; fax: +86 216 510 2412.
E-mail address: rhfan@fudan.edu.cn (R. Fan).

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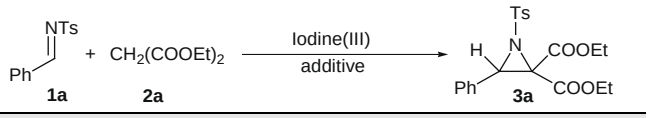
Table 1
Optimization of the oxidative cycloaddition of imine **1a** with diethyl malonate[a]



1a **2a** **3a**

Entry	Iodine (III) (equiv)	Additive (equiv)	Solvent	Time (min)	**3a**[b] (%)
1	$PhI(OCOCH_3)_2$ (2)	*t*-BuOK (1)	CH_3CN	60	0
2	$PhI(OCOCF_3)_2$ (2)	*t*-BuOK (1)	CH_3CN	60	0
3	PhIO (2)	*t*-BuOK (1)	CH_3CN	60	38
4	PhIO (2)	$BF_3{\cdot}Et_2O$ (1)	CH_3CN	60	0
5	PhIO (2)	*t*-BuOK (1)	H_2O	60	0
6	PhIO (2)	*t*-BuOK (1)	CH_3OH	60	0
7	PhIO (2)	*t*-BuOK (1)	*t*-BuOH	60	22
8	PhIO (2)	*t*-BuOK (1), KI (1)	CH_3CN	5	52
9	PhIO (2)	KI (1)	CH_3CN	5	85
10	PhIO (1)	KI (1)	CH_3CN	60	46
11	PhIO (3)	KI (1)	CH_3CN	5	84
12	PhIO (2)	KI (1)	Toluene	30	43
13	PhIO (2)	KI (1)	DMF	5	70
14	PhIO (2)	KI (1)	DMSO	5	62
15	PhIO (2)	KI (1)	THF	5	68
16	PhIO (2)	KI (0.5)	CH_3CN	5	92
17	PhIO (2)	KI (0.2)	CH_3CN	5	93
18	PhIO (2)	KI (0.1)	CH_3CN	30	82
19	PhIO (2)	KBr (1)	CH_3CN	60	0
20	PhIO (2)	KCl (1)	CH_3CN	60	0
21	PhIO (2)	KF (1)	CH_3CN	60	0
22	PhIO (2)	KOAc (1)	CH_3CN	60	0
23	$PhI(OCOCH_3)_2$ (2)	KI (1)	CH_3CN	60	0
24	$PhI(OCOCF_3)_2$ (2)	KI (1)	CH_3CN	60	0

[a] The reactions were performed with imine (0.5 mmol) and diethyl malonate (0.55 mmol) in anhydrous solvent (1 mL) at 25 °C.
[b] Isolated yields.

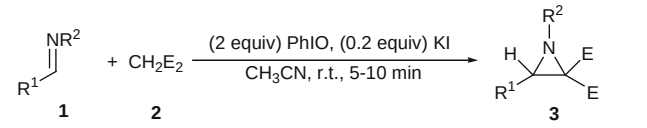
reactions of *N*-$Ph_2P(O)$-imine and *N*-*tert*-BuS(O)-imine. The reaction of aryl *N*-Ts imines was found to tolerate a range of different groups with different electronic demands on the aromatic rings involving electron-donating and electron-withdrawing groups. When *tert*-Bu-substituted *N*-Ts imine was employed, no desired aziridine was obtained. Sterically hindered di-*tert*-butyl malonate was also effective substrate for the reaction. The reactions with 2,4-pentanedione and ethyl acetoacetate afforded the corresponding products in good yields, while no aziridine was formed in the reactions with ethyl 2-cyano- and 2-nitro-acetate.

In order to understand the reaction pathway, several control experiments were done. The nucleophilic addition of diethyl malonate **2a** to *N*-Ts imine **1a** under basic conditions did not complete in 5 min, and only gave rise to the addition product **4a** in 14% yield (Scheme 2, Eq. 1). The intermolecular oxidative cyclization of **4a** under the same conditions required 4 h to complete the reaction, and affords product **3a** in 68% yield (Scheme 2, Eq. 2). After the reaction, the formation of I_2 was observed. However, no aziridine was formed when 0.5 equiv of I_2 was used as the replacement of KI.

In our previous studies on the oxidative cyclization reactions with $PhI(OAc)_2/Bu_4NBr$/*t*-BuOK system,[4a,c] a mechanism mediated by Br^+ or AcOBr has been hypothesized. However, the control experiments and the reaction without KI (Table 1, entry 3) indicated that this PhIO/KI-induced oxidative cycloaddition of imines with methylene compounds might not be mediated by I^+.[9] A plausible reaction pathway is outlined in Scheme 3. Polymeric iodosobenzene is depolymerized by KI to generate a reactive intermediate **A**,[7] which works as a base to deprotonate the activated methylene compound to afford an intermediate **B** and a nucleophilic anion of methylene compound. The electrophilic iodine center of intermediate **B** may act as a Lewis acid via a ligand exchange to promote the nucleophilic addition of the anion of methylene compound with imine to form an intermediate **C** with regeneration of KI. Subsequent reductive elimination of intermediate **C** yields the final aziridine **3**.

In conclusion, we have described an efficient oxidative cycloaddition of *N*-sulfonyl imines with methylene compounds using PhIO with a catalytic amount of KI.[10] The present procedure will provide a facile method for the synthesis of 2,2-difunctionalized aziridines

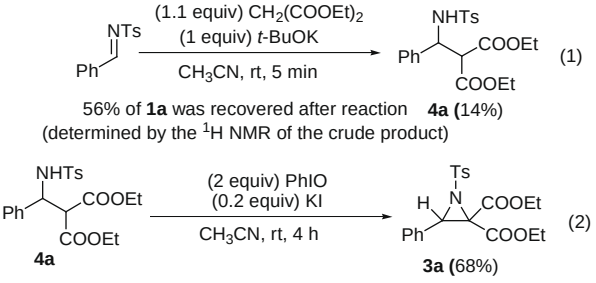
Table 2
PhIO/KI induced oxidative cycloaddition of imines with methylene compounds



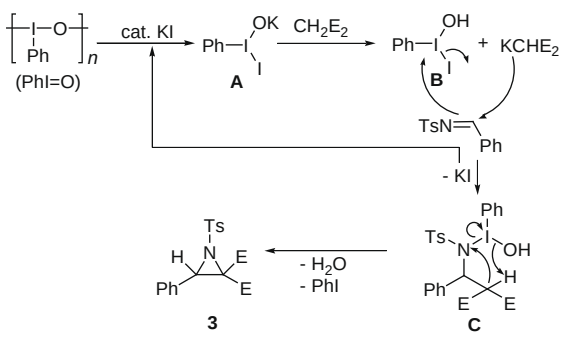
1 **2** **3**

Entry	R^1	R^2	CH_2E_2	**3**[a] (%)
1	Ph	Ts	$CH_2(COOEt)_2$	**3a** (93)
2	Ph	$PhS(O_2)$	$CH_2(COOEt)_2$	**3b** (91)
3	Ph	*p*-$ClC_6H_4S(O_2)$	$CH_2(COOEt)_2$	**3c** (86)
4	Ph	$CH_3S(O_2)$	$CH_2(COOEt)_2$	**3d** (95)
5	Ph	$Ph_2P(O)$	$CH_2(COOEt)_2$	**3e** (0)
6	Ph	*tert*-BuS(O)	$CH_2(COOEt)_2$	**3f** (0)
7	*p*-$CH_3C_6H_4$	Ts	$CH_2(COOEt)_2$	**3g** (96)
8	*m*-$CH_3C_6H_4$	Ts	$CH_2(COOEt)_2$	**3h** (91)
9	*p*-ClC_6H_4	Ts	$CH_2(COOEt)_2$	**3i** (93)
10	*o*-ClC_6H_4	Ts	$CH_2(COOEt)_2$	**3j** (95)
11	*o*-BrC_6H_4	Ts	$CH_2(COOEt)_2$	**3k** (86)
12	*p*-CNC_6H_4	Ts	$CH_2(COOEt)_2$	**3l** (95)
13	*p*-FC_6H_4	Ts	$CH_2(COOEt)_2$	**3m** (82)
14	*m*-$NO_2C_6H_4$	Ts	$CH_2(COOEt)_2$	**3n** (94)
15	1-Naphthyl	Ts	$CH_2(COOEt)_2$	**3o** (88)
16	*tert*-Bu	Ts	$CH_2(COOEt)_2$	**3p** (0)
17	Ph	Ts	$CH_2(COOCH_3)_2$	**3q** (91)
18	Ph	Ts	$CH_2(COOBu\text{-}tert)_2$	**3r** (86)
19	Ph	Ts	CH_3COCH_2COOEt	**3s** (78)
20	Ph	Ts	$CH_3COCH_2COCH_3$	**3t** (84)
21	Ph	Ts	NO_2CH_2COOEt	**3u** (0)
22	Ph	Ts	$CNCH_2COOEt$	**3v** (0)

[a] Isolated yields.



Scheme 2. Control experiments.



Scheme 3. A plausible reaction pathway.

under neutral conditions. Further studies on the application of this system are ongoing and will be reported in due course.

Acknowledgments

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10. General experimental procedure and spectroscopic data for **3a**: A solution of imine (0.5 mmol) and CH_2E_2 (0.55 mmol) in anhydrous CH_3CN was treated with PhIO (220 mg, 1 mmol) and KI (17 mg, 0.1 mmol). The resulting mixture was stirred at 25 °C. After imine disappeared (determined by TLC), the mixture was concentrated, and directly purified by flash column chromatography (10–20% ethyl acetate in hexane) to provide the corresponding aziridine. *Diethyl 3-phenyl-1-tosylaziridine-2,2-dicarboxylate* ***3a***: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 8.2 Hz, 2H), 7.35 (d, J = 8.2 Hz, 2H), 7.20–7.27 (m, 5H), 4.89 (s, 1H), 4.36–4.42 (m, 2H), 3.95 (q, J = 7.2 Hz, 2H), 2.44 (s, 3H), 1.37 (t, J = 7.1 Hz, 3H), 0.88 (t, J = 7.1 Hz, 3H).