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Diiodine–Triethylsilane System: Reduction of *N*-Sulfonyl Aldimines to *N*-Alkylsulfonamides

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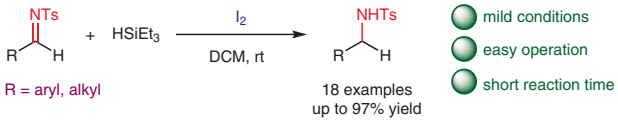

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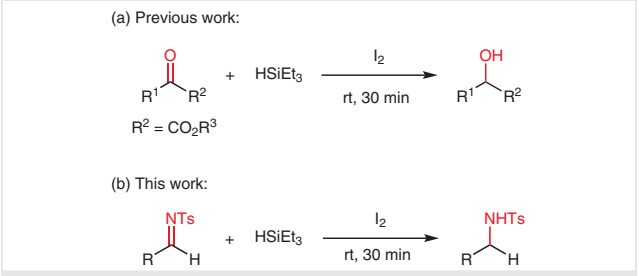
Abstract Because molecular iodine and hydrosilanes are stable to both air and moisture, reactions using these reagents are easy to operate and require mild reaction conditions. Molecular iodine and a hydrosilane were used to reduce *N*-sulfonyl aldimines to the corresponding *N*-alkylsulfonamides. This transformation is a practical method for the synthesis of *N*-alkylsulfonamides.

Key words imines, iodine, reduction, hydrosilanes, sulfonamides

Molecular iodine, a readily available, inexpensive, nontoxic, and easily handled reagent has been widely used in organic transformations in recent years, for example, in the functionalization of alkenes,[1] electrophilic cyclizations of alkynes,[2] C–N bond formation,[3] oxidative coupling reactions,[4] electrochemical oxidative cross-coupling reactions,[5] and cross-dehydrogenative coupling reactions.[6] In pursuit of our interest in molecular-iodine-mediated reduction reactions, we chose hydrosilanes as reducing agents because they also are easy to handle and inexpensive.[7] We surmised that reduction reactions employing diiodine and a hydrosilane would have the characteristics of mild reaction conditions and simple operations.

Several studies on I_2–hydrosilane systems have been reported. These include the preparation of alkyl iodides from carbonyl compounds,[8] the preparation of symmetrical ethers from carbonyl compounds,[9] and transformations in carbohydrate chemistry.[10] In a departure from these previous works, we recently reported the transformation of α-keto esters into the corresponding α-hydroxy esters by using a I_2–$HSiEt_3$ system, as an example of simple reduction application (Scheme 1a).[11] Here, we describe the application of an iodine–hydrosilane system in the reduction of aldimines (Scheme 1b). Hydrosilanes are frequently used for the reduction of imines to amines. The main catalysts used include metal catalysts[12] such as Ti, Re, Ru, Fe, Ir, Cu, Ni, or Zn and nonmetal catalysts such as boron compounds.[13] *N*-Alkylsulfonamides are an important class of nitrogen-containing compounds,[14] many of which display biological activities.[15] We therefore studied the synthesis of *N*-alkylsulfonamides from *N*-sulfonyl aldimines by reduction with hydrosilanes initiated by molecular iodine. Unlike existing methods,[16] the reduction of *N*-sulfonyl imines by iodine–hydrosilane systems does not require a metal and has a short reaction time.



Scheme 1 Reduction reactions using I_2–hydrosilane systems

Initially, we attempted to reduced *N*-[(1*E*)-benzylidene]-4-methylbenzenesulfonamide (**1a**; 1 equiv) by treatment with I_2 (0.5 equiv) and $HSiEt_3$ (2.0 equiv) in dichloromethane (2.0 mL) at room temperature for 30 minutes (Table 1, entry 1). To our delight, the desired reduction product, *N*-benzyl-4-methylbenzenesulfonamide (**2a**), was obtained in 68% yield. When another hydrosilane, 1,1,3,3-tetramethyldisiloxane (TMDS),[7] was tested, the yield decreased slightly (entry 2). We therefore chose $HSiEt_3$ as a reductant for our subsequent researches. Adjustment of the amount of I_2 showed that 0.5 equivalents of I_2 gave the best yield of 68% (entries 1, 3, and 4). Reducing the amount of $HSiEt_3$ to 1.5 equivalents gave a lower yield (entry 5). When

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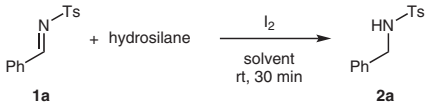
various common solvents (DCM, EtOAc, toluene, THF, EtOH, H_2O, and DMF) were screened, DCM was found to be the most effective for this transformation (entries 1 and 6–11).

Table 1 Optimization of the Reaction Conditions



1a **2a**

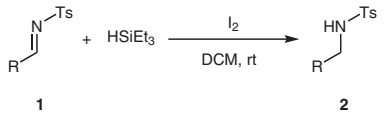
Entry	Hydrosilane	**1a**/hydrosilane/I_2 (equiv)	Solvent	Yield[a] (%)
1	$HSiEt_3$	1.0:2.0:0.5	DCM	68
2	TMDS	1.0:2.0:0.5	DCM	65
3	$HSiEt_3$	1.0:2.0:1.0	DCM	62
4	$HSiEt_3$	1.0:2.0:0.3	DCM	59
5	$HSiEt_3$	1.0:1.5:0.5	DCM	61
6	$HSiEt_3$	1.0:2.0:0.5	EtOAc	61
7	$HSiEt_3$	1.0:2.0:0.5	toluene	63
8	$HSiEt_3$	1.0:2.0:0.5	THF	–
9	$HSiEt_3$	1.0:2.0:0.5	EtOH	–
10	$HSiEt_3$	1.0:2.0:0.5	H_2O	–
11	$HSiEt_3$	1.0:2.0:0.5	DMF	–

[a] Isolated yield after purification by column chromatography.

With the optimized reaction conditions in hand, we reduced various *N*-tosyl aldimines with the I_2–$HSiEt_3$ system at room temperature to give the corresponding *N*-alkylsulfonamides (Table 2). Aromatic aldimines containing an electron-donating methoxy or methyl group at the *para*-position of the phenyl ring were competent substrates, giving sulfonamides **2b** and **2c** in yields of 57 and 90%, respectively (Table 2, entries 2 and 3). Aromatic aldimines with an electron-withdrawing methoxycarbonyl, nitro, or trifluoromethyl group at the *para*-position of the phenyl ring were also effective substrates, giving **2d**, **2e**, and **2f** in yields of 75, 94, and 70%, respectively (entries 4–6). Substrates with halo groups on the benzene rings also reacted well to give the corresponding products **1g–k** in moderate to excellent yields (entries 7–11). The reaction was not significantly affected by steric hindrance, because the yields from the *ortho*-substituted substrates **1k** and **1n** were higher than those from the corresponding *meta*-substituted substrate **1j** and **1m** (entries 10–13). The 1-naphthyl aldimine **1n** was also tolerated, giving the corresponding product **2n** in 71% yield (entry 14). Moreover, the 2-furyl aldimine **1o** was successfully reduced by the I_2–$HSiEt_3$ system, but gave a low yield (22%) of product **2o** (entry 15). Note that the alkyl aldimines **1p–r** also reacted well to give the desired products in excellent yields (entry 16–18).

We then examined the reactivity of a ketimine (Scheme 2). Ketimine **3** was effectively reduced by the I_2–$HSiEt_3$ system to give the desired product **4** in 90% yield.

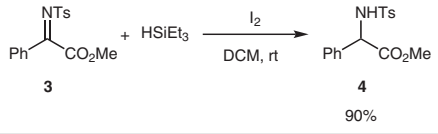
Table 2 Scope of the *N*-Tosyl Aldimine[a]



1 **2**

Entry	Substrate	R	Product[b]	Yield[c] (%)
1	**1a**	Ph	**2a**	68
2	**1b**	4-$MeOC_6H_4$	**2b**	57
3	**1c**	4-Tol	**2c**	90
4	**1d**	4-$MeO_2CC_6H_4$	**2d**	75
5	**1e**	4-$O_2NC_6H_4$	**2e**	94
6	**1f**	4-$F_3CC_6H_4$	**2f**	70
7	**1g**	4-FC_6H_4	**2g**	72
8	**1h**	4-BrC_6H_4	**2h**	81
9	**1i**	4-ClC_6H_4	**2i**	91
10	**1j**	3-ClC_6H_4	**2j**	75
11	**1k**	2-ClC_6H_4	**2k**	97
12	**1l**	3-Tol	**2l**	60
13	**1m**	2-Tol	**2m**	67
14	**1n**	1-naphthyl	**2n**	71
15	**1o**	2-furyl	**2o**	22
16	**1p**	Cy	**2p**	93
17	**1q**	Bu	**2q**	90
18	**1r**	*i*-Bu	**2r**	94

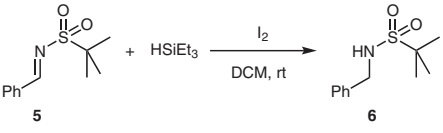
[a] Reaction conditions: imine **1** (1.0 mmol, 1.0 equiv), $HSiEt_3$ (2.0 mmol, 2.0 equiv), I_2 (0.5 mmol, 0.5 equiv), DCM (2.0 mL), rt, 30 min.
[b] All the products were identified by comparison of their analytical data with those reported in the literature.
[c] Isolated yield after purification by column chromatography.



3 **4**
90%

Scheme 2 Reduction of ketimine **3** by using the I_2–$HSiEt_3$ system

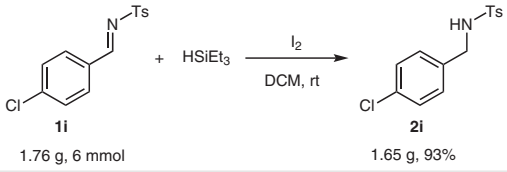
Next, another type of *N*-sulfonyl imine was tested (Scheme 3). The *N-tert*-butylsulfonyl imine **5** participated well in this reaction, giving the corresponding sulfonamide **6** in 85% yield.



5 **6**
85%

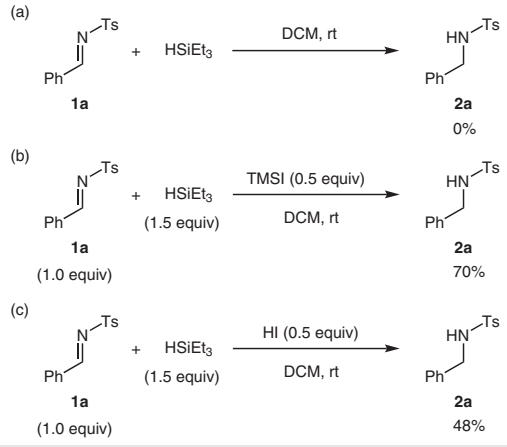
Scheme 3 Reduction of the *N-tert*-butylsulfonyl imine **5** by using the I_2–$HSiEt_3$ system

To illustrate the synthetic applications of the I_2–$HSiEt_3$ system in the reduction of *N*-sulfonyl imines, we carried out a large-scale reaction to produce 1.65 g of *N*-(4-chlorobenzyl)-4-methylbenzenesulfonamide (**2i**) in 93% yield (Scheme 4).



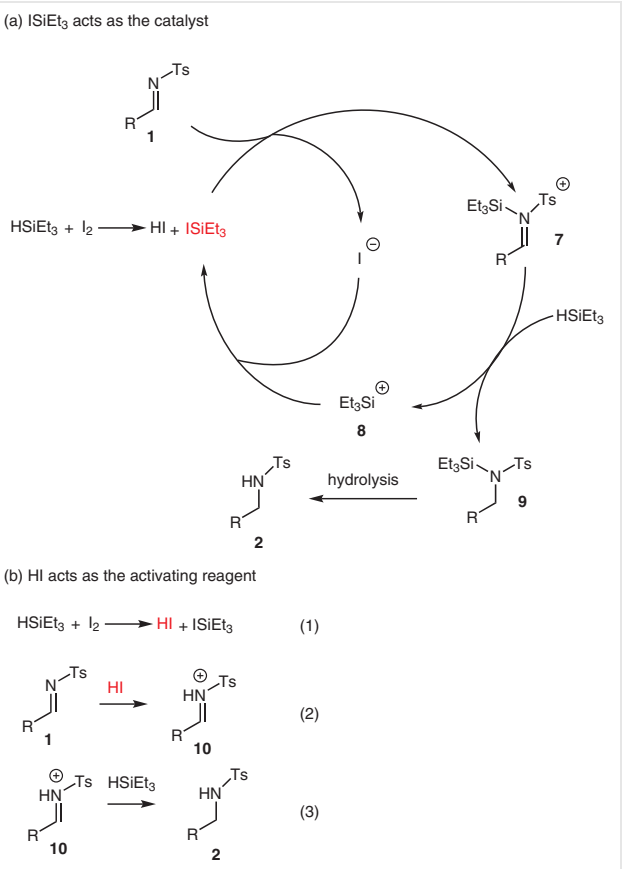
Scheme 4 Large-scale preparation of **2i**

To investigate the reaction mechanism, we conducted several experiments (Scheme 5). First, reduction of imine **1a** by $HSiEt_3$ without I_2 did not proceed, and the starting material remained unreacted (Scheme 5a). It is known that I_2 can react with $HSiEt_3$ to produce HI and $ISiEt_3$.[8,17] In the reduction of α-keto esters with the I_2–$HSiEt_3$ system, $ISiEt_3$ proved to be the actual catalyst.[11] We suspected that $ISiEt_3$ might also be the catalyst in the reduction of *N*-sulfonyl imines with the I_2–$HSiEt_3$ system. To test this hypothesis, iodo(trimethyl)silane (TMSI), a commercially available reagent, was used, and *N*-sulfonyl imine **1a** was successfully reduced to **2a** in 70% yield (Scheme 5b). However, product **2a** was also obtained in 48% yield when HI was used (Scheme 5c), so the reduction might be promoted by the presence of HI.



Scheme 5 Control experiments

Based on these results, two possible reaction mechanism are proposed (Scheme 6). If $ISiEt_3$ acts as the catalyst (Scheme 6a), I_2 first reacts with $HSiEt_3$ to produce HI and $ISiEt_3$. The *N*-sulfonyl imine **1** then reacts with $ISiEt_3$ to generate the silylated iminium ion **7**[18] and an iodine anion. Iminium ion **7** is then reduced by another molecule of $HSiEt_3$ to form the silylated amine **9** and $ISiEt_3$. The $ISiEt_3$ might be generated from an iodine anion and the intermediate silylenium ion **8**.[19] Finally, product **2** is formed through hydrolysis of the silylated amine **9**.[13b] On the other hand, if HI acts as the activating reagent (Scheme 6b), I_2 first reacts with $HSiEt_3$ to produce HI and $ISiEt_3$. The *N*-sulfonyl imine **1** is then protonated to form intermediate **10**, which is reduced by $HSiEt_3$ to give product **2**.



Scheme 6 Possible reaction mechanisms

In conclusion, we have reported a novel metal-free protocol for the synthesis of *N*-alkyl sulfonamides from *N*-sulfonyl aldimines under mild conditions.[20] In this transformation, imines are reduced by $HSiEt_3$ with initiation by molecular iodine. This reaction is the first report of the reduction of imines by using an I_2–hydrosilane system, and it might serve as a practical method for the synthesis of *N*-alkylsulfonamides.

Funding Information

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1706544.

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(20) ***N*-Benzyl-4-methylbenzenesulfonamide (2a); Typical Procedure**
A flask was successively charged with $HSiEt_3$ (232.6 mg, 2.0 mmol, 2.0 equiv), *N*-sulfonyl aldimine **1a** (259.3 mg, 1.0 mmol, 1.0 equiv), DCM (2.0 mL), and I_2 (126.9 mg, 0.5 mmol, 0.5 equiv), and the mixture was stirred at rt for 30 min. DCM (20.0 mL) and 0.5 M aq $Na_2S_2O_3$ (10 mL) were added to the flask, and the organic layer was separated, washed with brine, dried (Na_2SO_4), filtered, concentrated, and purified by flash column chromatography [silica gel (200–300 mesh), PE–EtOAc (4:1)] to give a white solid; yield: 178.2 mg (68%); mp 117–118 °C.
^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.75 (d, *J* = 8.4 Hz, 2 H), 7.30 (d, *J* = 8.4 Hz, 2 H), 7.28–7.23 (m, 3 H), 7.22–7.16 (m, 2 H), 4.93–4.80 (m, 1 H), 4.11 (d, *J* = 6.6 Hz, 2 H), 2.44 (s, 3 H). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 143.6, 136.9, 136.4, 129.9, 128.8, 128.0, 127.3, 47.4, 21.7.