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2-(*N*-Hydroxylamino) sulfone synthesis by indium–iodine-triggered aza-Michael type addition of nitroarenes to vinyl sulfones

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ABSTRACT

One-pot reduction-triggered 1,4-addition reaction of various nitroarenes to the α,β-unsaturated sulfones was investigated. In the presence of indium/iodine in MeOH at room temperature, nitroarenes reduced in situ reacted with vinyl sulfones and produced β-(*N*-hydroxylamino) sulfones in good yields.

C–N bond formation derived from the aza-Michael additions of amines or Michael additions of cyano compounds to conjugated alkenones has been developed as a valuable synthetic tool for the synthesis of β-aminocarbonyl or β-cyanocarbonyl compounds.[1] Various examples of aza-Michael addition reactions under milder conditions using various catalysts were recently shown in the literature.[2] Those catalysts or promoters include palladium,[2a] BiX_3 (X = NO_3, OTf),[2b,2c] silica gel,[2d] Cu-nanoparticles,[2e] ionic liquids,[2f] CAN,[2g] microwave irradiation,[2h] water,[2i] DBU,[2j] Amberlyst-15,[2k] and pyrrolidine–thiourea.[2l] In addition, the Michael addition reactions to vinyl sulfones are also well documented, as sulfones can act as good activating groups for C–C bond-forming reactions.[1] However, the aza-Michael addition reactions to vinyl sulfones are barely studied. The recent application of aza-Michael addition reactions for the preparation of amino sugars [3] proves the usefulness of the reaction. In addition, double aza-Michael addition to vinyl sulfone moieties was utilized for thiomorpholine 1,1-dioxide ring formation,[4a] which is important for macrocyclic systems[4b] or is a valuable sub-unit of an antibacterial agent.[4c] Those previous studies encouraged us to attempt a new type of aza-Michael addition of nitroarenes to vinyl sulfones, that is, a one-pot reduction-triggered process involving the reduction of nitroarenes and subsequent 1,4-addition to vinyl sulfones.

In our previous study of indium-mediated reductive heterocyclizations of nitroarenes,[5] it was found that reduced nitro groups can trigger heterocyclization toward nitrogen-containing heterocycles, such as 2,1-benzisoxazoles,[5a] benzimidazoles,[5b] quinolines,[5c] indazoles,[5d,e] and indoles,[5f] when there is a proper functional group at the *ortho* position. These reactions are noteworthy as indium has been receiving increasing attention due to environmental issues and the ease of reactions that obviate the need for inflammable anhydrous organic solvents and inert atmosphere.[6b] However, the indium-mediated reactions we developed previously were mostly intramolecular, one-pot reductive reactions followed by the C–N bond formation.

Building upon this concept, one-pot intermolecular reactions between nitroarenes and Michael acceptors may also be possible if the reaction conditions are properly controlled. Thus, here we decided to investigate more challenging intermolecular one-pot aza-Michael type addition reactions of nitroarenes to vinyl sulfones, which can be a useful synthetic tool for making β-(*N*-hydroxylamino) sulfones.

As mentioned above, our previous reductive heterocyclizations of nitroarenes were accomplished via the reductive reaction of the nitro group followed by cyclization to the properly *ortho*-substituted neighboring functional group. Similar to this intramolecular reaction, the intermolecular type of the one-pot reductive 1,4-addition reaction should be possible via (1) triggering with the reductive reaction of the nitro group and (2) the 1,4-addition of in situ formed nitrogen nucleophile to the α,β-unsaturated substrate, if the timing of the reduction versus the in situ formed nitrogen nucleophile to the α,β-unsaturated substrate is well managed. Thus, we decided to examine the indium-mediated one-pot 1,4-addition reaction of nitroarenes with the α,β-unsaturated substrate. α,β-Unsaturated sulfones were selected as model compounds because (1) they are excellent Michael acceptors for a number of nucleophiles such as amines, alcohols, and thiols and (2) the resulting β-amino sulfone products are of interest for physiological processes. Nevertheless, their synthetic methods are relatively poorly documented in the literature.

Thus, to discover the appropriate reaction conditions for the reduction-triggered aza-Michael addition of nitroarenes to vinyl sulfones, 1,4-addition reaction of nitrobenzene to methyl vinyl sulfone was examined using indium and a wide range of Lewis acids or acid additives such as $InCl_3$, I_2, AcOH, and HI in various solvent systems. Most of the reactions failed to show aza-Michael addition products such as β-amino sulfone as a major product. In the case of

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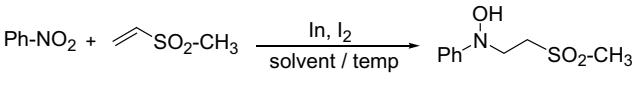
Table 1
Indium-mediated reductive aza-Michael type addition of nitrobenzene to methyl vinyl sulfone under various conditions



1 **2**

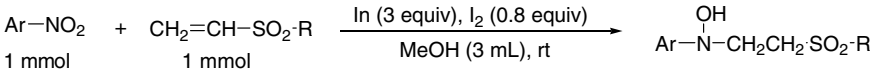
Entry	Molar equiv				Solvent (mL)/temp (°C)	Time (h)	Yield[a] (%)
	1	In	I_2	**2**			
1	1	3	0.8	1	CH_2Cl_2(3)/rt	24	Trace[b]
2	1	3	0.8	1	THF(3)/rt	24	Trace[b]
3	1	2	0.8	1	MeOH(3)/rt	24	Trace[b]
4	1	3	0.8	1	MeOH(3)/rt	6	82 (77)[c]
5	1	4	0.8	1	MeOH(3)/rt	6	86
6	1	3	0.8	1	MeOH(3)/50	4	73
7	1	3	0.8	1	MeOH(10)/rt	6	76
8	1	3	0.4	1	MeOH(3)/rt	24	68
9	1	3	1.2	1	MeOH(3)/rt	5	69
10	1	3	0.8	1.5	MeOH(3)/rt	5	78
11	1	3	0.8	2	MeOH(3)/rt	5	54
12	1	3	0.8	1	MeOH(10)/50	6	56
13	1	3	0.8	1	MeOH(3)–H_2O(6)/rt	24	49
14	1	3	0.8	1	H_2O(10)/rt	16	43

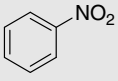
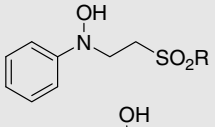
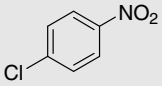
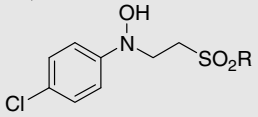
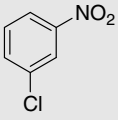
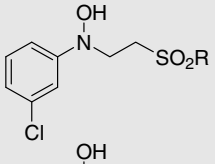
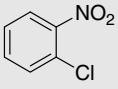
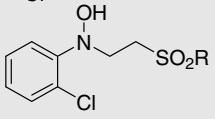
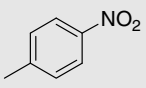
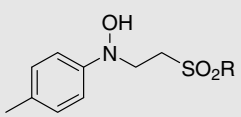
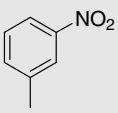
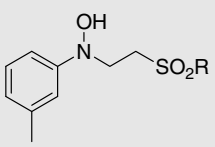
[a] NMR yield with an internal standard.
[b] Substrate (**1**, 1 mmol) was recovered (entry 1: 82%, entry 2: 76%, entry 3: 40%).
[c] Isolated yield.

$InCl_3$, the starting substrate was recovered typically with a low yield of the 1,4-addition product [less than 15% at most; nitrobenzene (1 equiv)/vinyl sulfone (1 equiv)/indium (4 equiv)/$InCl_3$ (0.4 equiv) in THF/H_2O (v/v = 5/1) at 50 °C]. In the case of AcOH and HI [AcOH in MeOH at reflux and aqueous HI in benzene/1 drop of aliquat 336 at reflux], the starting substrate disappeared after several hours and the reaction produced lots of by-products without the desired major products, presumably because of undesired polymerization. However, some of the indium–iodine-mediated reactions produced major products, which were seemingly the expected 1,4-addition products of methyl vinyl sulfone and were isolated by filtration, extraction, and flash column chromatography. Unexpectedly, it was not *N*-[2-(methylsulfonyl)ethyl]benzenamine, that is, β-amino sulfone that was formed, but a different type of product. Interestingly enough, it was instead the *N*-hydroxy-*N*-[2-(methylsulfonyl)ethyl]benzenamine, β-(*N*-hydroxylamino) sulfone, which is rarely seen in the literature. Indium metal may initiate the reaction via a single electron transfer (SET) reaction to the nitro group, which may result in a nitroso intermediate. Then, repeated SET reaction of the *in situ* formed radical anion species of nitrosobenzene, *prior to conversion to the amino group*, may attack the electron-deficient olefin of the vinyl sulfone to form the β-(*N*-hydroxylamino) sulfone, which is stable enough to isolate by conventional column chromatography.

Although β-(*N*-hydroxylamino) sulfones are not well documented, such compounds have both *N*-hydroxylamine and sulfone

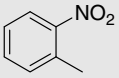
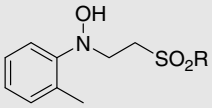
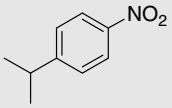
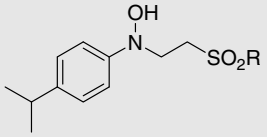
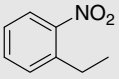
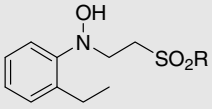
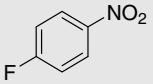
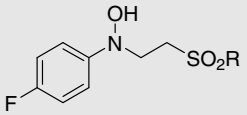
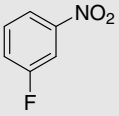
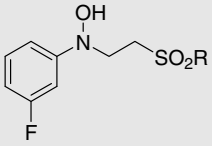
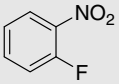
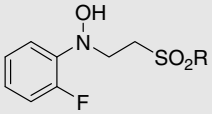
Table 2
Indium–iodine-triggered aza-Michael type addition of various nitroarenes (1 mmol) to vinyl sulfones (1 mmol) in the presence of indium (3 equiv), iodine (0.8 equiv) in methanol at room temperature



Entry	Ar–NO_2	R	Time (h)	Product	Yield[a] (%)
1		CH_3	6		77
2		CH_2CH_3	5		74
3		Ph	7		65
4		CH_3	5		77
5		CH_2CH_3	5		65
6		Ph	6		70
7		CH_3	9		66
8		CH_2CH_3	5		64
9		Ph	5		74
10		CH_3	7		77
11		CH_2CH_3	5		77
12		Ph	12		80
13		CH_3	5		62
14		CH_2CH_3	6		67
15		Ph	9		37 (72)[b]
16		CH_3	8		51
17		CH_2CH_3	5		60
18		Ph	8		47 (65)[b]

(*continued on next page*)

Table 2 (*continued*)

Entry	Ar–NO_2	R	Time (h)	Product	Yield[a] (%)
19		CH_3	8		77
20		CH_2CH_3	10		88
21		Ph	9		74
22		CH_3	7		55
23		CH_2CH_3	4		74
24		Ph	11		34 (74)[b]
25		CH_3	8		82
26		CH_2CH_3	8		69
27		Ph	8		83
28		CH_3	4		78
29		CH_2CH_3	4		69
30		Ph	6		68
31		CH_3	6		83
32		CH_2CH_3	7		76
33		Ph	12		66
34		CH_3	7		70
35		CH_2CH_3	12		78
36		Ph	9		59

[a] Isolated yield.
[b] NMR yield with an internal standard.

groups in a molecule and have been reported in the recent literature as drug-like compounds[7] or as potent inhibitors of matrix metalloproteinases.[8] Most early examples[9] shown in the literature focused on physical structural study rather than their application to chemical or biological systems presumably because synthetic methodology for β-(*N*-hydroxylamino) sulfone derivatives was poorly developed. Thus, new synthetic methods for β-(*N*-hydroxylamino) sulfone and tests on their biological and/or chemical activities are merited. Therefore, various reaction conditions were carefully reinvestigated to optimize the reactions for the formation of *N*-hydroxy-*N*-[2-(methylsulfonyl)ethyl]benzenamine, instead of the typical aza-Michael addition product, *N*-[2-(methylsulfonyl)ethyl]benzenamine. The selected control experiments are summarized in Table 1.

As shown in Table 1, reactions in aprotic solvent (entries 1 and 2) did not proceed well and mostly starting substrates were recovered. However, by using protic solvents such as methanol and/or water, the desired β-(*N*-hydroxylamino) sulfone was obtained as a major product. Usually, methanol was better than the methanol/water co-solvent (entry 13) and/or water (entry 14) presumably because of the poor solubility of nitroarene and vinyl sulfone substrates. Thus, after the various reaction conditions were examined, nitrobenzene (1 equiv)/vinyl sulfone (1 equiv)/indium (3 equiv)/iodine (0.8 equiv) in methanol at room temperature (entry 4) was deemed optimal in terms of yield and cost-effectiveness.

As indium in the presence of iodine in methanol turned out to have a reductive ability for nitroarene, and given that the reduced intermediate can trigger the aza-Michael type 1,4-addition to vinyl sulfone with a reasonable yield, we next applied the optimized reaction conditions to various substrates to test for general synthetic utility. Thus, the aza-Michael type 1,4-addition of variously substituted nitroarenes to selected vinyl sulfones (CH_2=CH–SO_2–R, where R = methyl, ethyl, phenyl) was examined, and the results are shown in Table 2. In most cases, the aza-Michael type 1,4-addition appears to be generally applicable, as most of the substrates were consumed within 4–11 h to give the corresponding β-(*N*-hydroxylamino) sulfones with reasonable yields. As shown in Table 2, most reactions performed with different nitrobenzene derivatives seemed to be unaffected by the substitution. Electron-donating or electron-withdrawing groups did not show drastic influence on product yield. Moreover, more or less sterically hindered substrates such as 2-nitrotoluene (entries 19–21) or 1-ethyl-2-nitrobenzene (entries 25–27) proceeded well and produced β-(*N*-hydroxylamino) sulfones without retardation of the reaction or yield reduction. Some of severe drops in the isolated yields (for example, entries 15, 18, and 24) are attributed to difficulties in separation from overlapped residual phenyl vinyl sulfone (~5–10%) that have almost the same R_f values with products, not because of problems with reactivity, which is proven by their NMR yields (entries 15, 18, and 24). The structures of β-(*N*-hydroxylamino) sulfones were fully characterized by ^{1}H NMR, ^{13}C NMR, FTIR, MS, HRMS.[10] Furthermore, the structure of a representative compound, 2-chloro-*N*-hydroxy-*N*-[2-(phenylsulfonyl)ethyl]benzenamine, was reconfirmed by X-ray crystallography as the product is somewhat unexpected new type of material that is rarely known.[10] The molecular structure with an atom-labeling scheme is shown in Figure 1.

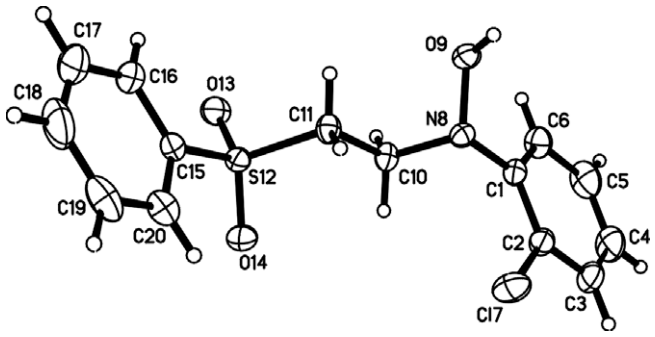


Figure 1. Molecular structure of 2-chloro-*N*-hydroxy-*N*-[2-(phenylsulfonyl)-ethyl]benzenamine with an atom-labeling scheme.

A typical procedure for aza-Michael type addition reactions is as follows. Nitroarene (1 mmol) was added to a mixture of indium powder (345 mg, 3.0 mmol) and iodine (203 mg, 0.8 mmol) in MeOH (1 mL), and then vinyl sulfone (1 mmol) in MeOH (2 mL) was added. The reaction mixture was stirred at room temperature under a nitrogen atmosphere. After the reaction was complete, it was diluted with diethyl ether (30 mL), filtered through Celite, poured into saturated aqueous $NaHCO_3$ solution (30 mL), and extracted with diethyl ether (30 mL × 3). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. The residue was eluted with ethyl acetate/hexane (v/v = 30/70) via silica gel (230–400 mesh) flash column chromatography to give the corresponding β-(*N*-hydroxylamino) sulfone.

In conclusion, we have described a simple and efficient method for one-pot reduction-triggered 1,4-addition reaction of various nitroarenes to α,β-unsaturated sulfones, forming the corresponding β-(*N*-hydroxylamino) sulfone with good yields in the presence of indium and iodine in methanol. These findings may serve as a foundation for the development of new types of molecules.

Acknowledgments

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References and notes

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10. Representative spectroscopic data of 2-chloro-*N*-hydroxy-*N*-[2-(phenylsulfonyl)ethyl]benzenamine; mp 117–118.5 °C; TLC (30% ethyl acetate/hexane) R_f 0.27; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (dd, 2H, J = 7.4, 1.2 Hz), 7.69–7.65 (m, 1H), 7.58–7.51 (m, 3H), 7.29–7.20 (m, 2H), 7.07 (td, 1H, J = 7.4, 1.6 Hz), 6.31 (s, 1H), 3.55–3.45 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.2, 138.9, 133.9, 130.0, 129.3, 127.9, 127.5, 126.2, 125.4, 120.7, 53.2, 52.6; IR (KBr) 3383, 3074, 2996, 2937, 1579, 1442, 1309, 1278, 1144 cm^{-1}; GC–MS *m*/*z* (rel. intensity) 295 (M^+−16, 32), 153 (100), 135 (56), 118 (54), 99 (11), 77 (30); HRMS (EI) calcd for $C_{14}H_{14}ClNO_3S$ 311.0383, found 311.0387. CCDC 702263 contains the supplementary crystallographic data for this compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.