A Facile One-Flask Conversion of Aldehydes and Ketones to *N*-Sulfonyl Imines

Gunda I. Georg,* Geraldine C. B. Harriman, and Scott A. Peterson

Department of Medicinal Chemistry, University of Kansas, Lawrence, Kansas 66045

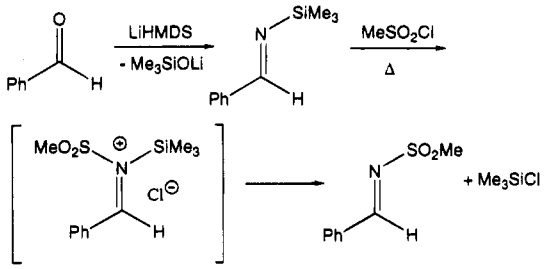
Received February 28, 1995

The use of *N*-sulfonyl imines in organic chemistry continues to expand as these substrates find utility as electron deficient 1,3-azabutadiene equivalents in inverse electron demand Diels–Alder chemistry,[1-6] as electrophilic aza-aldehyde equivalents in addition reactions,[7] as reactive olefin equivalents in ene reactions,[8,9] or as precursors to *N*-sulfonyloxaziridines which have utility as chiral oxidants.[10] Several methods for the preparation of *N*-sulfonyl imines have appeared in the literature. These methods include utilization of tellurium metal and chloramine,[11] rearrangement of oxime *O*-sulfinates,[12] Lewis acid-promoted reaction of sulfonamides with aldehydes or acetals,[13-16] or addition of *N*-sulfinyl sulfonamides to aldehydes in the presence of $BF_3{\cdot}Et_2O$.[6]

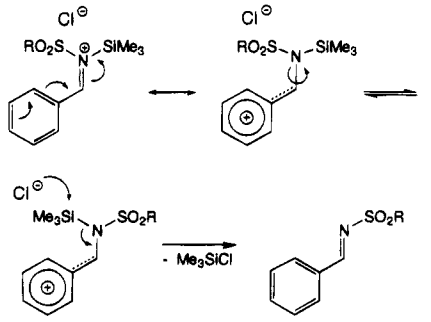
We herein report on the novel synthesis of *N*-sulfonyl imines via a halogen mediated conversion of *N*-(trimethylsilyl) imines in the presence of the appropriate sulfonyl chloride. This methodology circumvents various drawbacks of the aforementioned approaches such as the necessity of using large stoichiometric excesses of reagents, utilization of metals or extremely moisture sensitive reagents, limitations to producing aldimines only, and the use of anhydrous purification techniques. This approach is also quite concise since the *N*-sulfonyl imine is synthesized in a two-step one-flask conversion from the starting aldehyde or ketone. No purification of the *N*-sulfonyl imines is necessary as the conversions are quantitative and the byproducts of the reaction are volatile.

Various aldehydes and ketones were converted to their *N*-sulfonyl imines in excellent yields and high purity. The aldehydes or ketones are initially converted to their *N*-(trimethylsilyl) imines (Scheme 1) by the Hart procedure[17] utilizing lithium hexamethyldisilazide. These

Scheme 1



Scheme 2



imines are easily purified by vacuum distillation and are reacted stoichiometrically with the appropriate sulfonyl chloride to afford the *N*-sulfonyl imines and the volatile byproduct, trimethylsilyl chloride. Removal of the solvent and TMSCl afforded the pure *N*-sulfonyl imines.

The reaction produces only one isomer, which is the thermodynamically favored (*E*)-sulfonyl imine.[18] This can be rationalized through a resonance stabilized intermediate shown in Scheme 2. Iminium formation is followed by resonance stabilization through the extended π system. Rotation about the C–N bond allows for the appropriate arrangement necessary for the facile addition–elimination sequence to occur which affords the (*E*)-*N*-sulfonyl imine and trimethylsilyl chloride.

The (*E*)-imine geometries of *N*-(trimethylsilyl)benzaldimine (**2a**) and *N*-(methanesulfonyl)benzaldimine (**3a**) were proven through NOE studies. A 5.2% enhancement in the imine proton resonance was achieved after irradiation of the trimethylsilyl protons of **2a** (Figure 1). A 1.6% NOE enhancement was observed for the imine proton of **3a** after irradiation at the methanesulfonyl resonance.

As shown in Table 1, the appropriate *N*-(trimethylsilyl) imines were heated in the presence of stoichiometric quantities of either methanesulfonyl chloride or *p*-toluenesulfonyl chloride. A variety of solvents were utilized to achieve optimal conversion conditions. In some cases the conversion rates were sluggish. It was found that the reaction proceeded smoothly and quickly with neat reagents at a temperature of approximately 100 °C. Examples of this approach are summarized in Table 1.

In the first example benzaldehyde (**1a**) was converted to its *N*-(trimethylsilyl)aldimine **2a** quantitatively as determined by ^1H NMR and isolated in 63% yield after vacuum distillation. Imine **2a** was then heated in the presence of methanesulfonyl chloride at reflux in $CHCl_3$ which resulted in a quantitative conversion to **3a**. However, the conversion of **2a** to the corresponding *N*-(*p*-toluenesulfonyl) imine **3b** in $CHCl_3$ at reflux did not yield

(1) For the first Diels–Alder reaction with *N*-sulfonyl imines, see: Albrecht, R.; Kresze, G. *Chem. Ber.* **1964**, *97*, 490.
(2) For a review on early work, see: Boger, D. L.; Weinreb, S. N. *Hetero Diels–Alder Methodology in Organic Synthesis*; Academic: San Diego, 1987.
(3) Boger, D. L.; Kasper, A. M. *J. Am. Chem. Soc.* **1989**, *111*, 1517.
(4) Boger, D. L.; Corbett, W. L.; Curran, T. T.; Kasper, A. M. *J. Am. Chem. Soc.* **1991**, *113*, 1713.
(5) Sisko, J.; Weinreb, S. M. *Tetrahedron Lett.* **1989**, *30*, 3037.
(6) For an asymmetric version, see: McFarlane, A. K.; Thomas, G.; Whiting, A. *Tetrahedron Lett.* **1993**, *34*, 2379.
(7) Sisko, J.; Weinreb, S. M. *J. Org. Chem.* **1990**, *55*, 393.
(8) Tschaen, D. M.; Turos, E.; Weinreb, S. M. *J. Org. Chem.* **1984**, *49*, 5058.
(9) Melnick, M. J.; Freyer, A. J.; Weinreb, S. M. *Tetrahedron Lett.* **1988**, *29*, 3891.
(10) Davis, F. A.; Reddy, R. T.; Reddy, R. E. *J. Org. Chem.* **1992**, *57*, 6387.
(11) Trost, B. M.; Marrs, C. *J. Org. Chem.* **1991**, *56*, 6468.
(12) Boger, D. L.; Corbett, W. L. *J. Org. Chem.* **1992**, *57*, 4777 and references cited therein.
(13) Jennings, W. B.; Lovely, C. J. *Tetrahedron Lett.* **1988**, *29*, 3725.
(14) Jennings, W. B.; Lovely, C. J. *Tetrahedron* **1991**, *47*, 5561.
(15) Glass, R. S.; Hoy, R. C. *Tetrahedron Lett.* **1976**, *21*, 1781.
(16) Albrecht, R.; Kresze, G.; Mlakar, B. *Chem. Ber.* **1964**, *97*, 483.
(17) Hart, D. J.; Kanai, K.; Thomas, D. G.; Yang, T.-K. *J. Org. Chem.* **1983**, *48*, 289.
(18) Fraser, R. R.; Banville, J. *J. Chem. Soc., Chem. Commun.* **1979**, 47.

0022-3263/95/1960-7366$09.00/0 © 1995 American Chemical Society

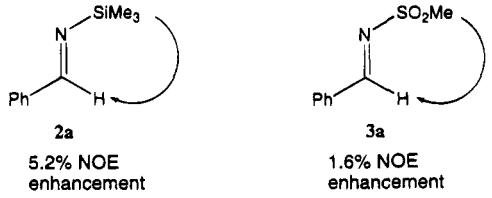
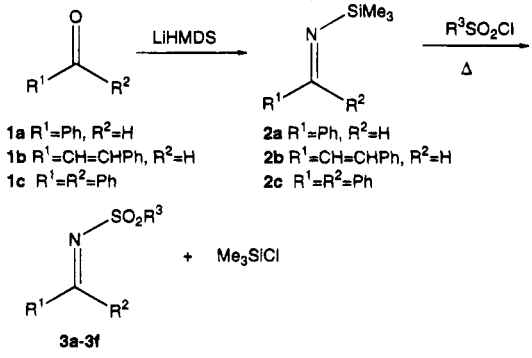


Figure 1. NOE experiments with imines **2a** and **3a**.

Table 1. Reaction Conditions and Yields for the Formation of *N*-Sulfonyl Imines 3a–f[a]



product 3	R^1	R^2	R^3	reflux solvent	*N*-sulfonyl imine (% conversion)
3a	Ph	H	Me	$CHCl_3$	100
3b	Ph	H	*p*-Tol	$CHCl_3$	0
3b	Ph	H	*p*-Tol	toluene	50
3b	Ph	H	*p*-Tol	neat	100
3c	CH=CHPh	H	Me	$CHCl_3$	65
3c	CH=CHPh	H	Me	toluene	100
3d	CH=CHPh	H	*p*-Tol	$CHCl_3$	35
3d	CH=CHPh	H	*p*-Tol	toluene	80
3d	CH=CHPh	H	*p*-Tol	neat	100
3e	Ph	Ph	Me	$CHCl_3$	61
3e	Ph	Ph	Me	toluene	100
3f	Ph	Ph	*p*-Tol	toluene	64
3f	Ph	Ph	*p*-Tol	neat	100

[a] Conversion percentages reflect the ratio of product to starting *N*-(trimethylsilyl) imine as determined by ^1H NMR.

any product. Replacing $CHCl_3$ with toluene as the solvent resulted in a 50% conversion of starting material to product after 24 h at reflux. Complete conversion was achieved when **2a** was warmed neat at 100 °C for 1 h in the presence of *p*-toluenesulfonyl chloride. These reaction conditions are convenient because no anhydrous solvents are necessary and removal of solvents is avoided.

Cinnamaldehyde (**1b**) was converted to its *N*-(trimethylsilyl) imine **2b** quantitatively as determined by ^1H NMR. The resulting crude imine was then converted to its *N*-sulfonyl imines **3c** and **3d**. It was found that the solvent of choice for the conversion to the *N*-(methanesulfonyl) imine **3c** was toluene while the neat reaction of **2b** with *p*-toluenesulfonyl chloride proceeded with quantitative conversion to afford the *N*-tosyl imine **3d**. In this approach the trimethylsilyl chloride byproduct becomes useful as it reacts stoichiometrically with the lithiated trimethylsilanol generated in the formation of the *N*-(trimethylsilyl) imine to provide a volatile bis-silyl product. This exemplifies the utility of this approach as all imines can be utilized as their crude products, because the lithium trimethylsilanolate byproduct of the trimethylsilyl imine formation will be converted to a volatile ether. The only remaining entity other than the desired product is inert lithium chloride.

N-(Trimethylsilyl) imine **2c** was prepared from benzophenone (**1c**) in 59% yield. The conversion to its *N*-(methanesulfonyl) imine **3e** proved to be successful in toluene, while *N*-(*p*-toluenesulfonyl) imine **3f** was formed utilizing neat reagents. Both reactions proceeded with quantitative conversion. It is interesting to note that the ^{13}C spectrum of **3f** at rt showed a broad multipletlike peak in the aromatic region, presumably due to hindered rotation of the phenyl moieties. A resolved spectrum of the imine was obtained at −40 °C.

This chemistry was applied unsuccessfully toward the synthesis of enolizable *N*-sulfonylaldimines and ketimines. The *N*-(trimethylsilyl) imines were generated at −40 °C, but subsequent warming in the presence of sulfonyl chlorides to form the *N*-sulfonyl imines led to undesired products. This is probably due to the fact that enolizable *N*-(trimethylsilyl) imines are unstable at temperatures above −10 °C.[19] Also it is interesting to note that attempts at the synthesis of nonconjugated nonenolizable *N*-sulfonyl imines proved unsuccessful (i.e. conversion of trimethylacetaldehyde to its corresponding *N*-sulfonyl imines). This result may be explained by the inability of the substrate to stabilize a carbocation intermediate via resonance in the transition states shown in Scheme 2.

Experimental Section

General. For general experimental information please see reference 20.

Synthesis of *N*-Trimethylsilyl Imines 2a–c (as described in reference 17). To cold (0 °C) hexamethyldisilazane (10.0 mmol) under an inert atmosphere was added dropwise 2.5 M *n*-BuLi in hexanes (9.5 mmol). The aldehyde (0.95 mmol) was then added to the cold LiHMDS solution, and the reaction was stirred at 0 °C for 30 min. The reaction was brought to room temperature, and the products were purified by vacuum distillation, although purification is not necessary.

***N*-(Trimethylsilyl)benzaldimine (2a)**:[17] ^1H NMR (300 MHz, $CDCl_3$) δ 0.28 (s, 9H), 7.44–7.46 (m, 3H), 7.80–7.83 (m, 2H), 9.00 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −1.2, 128.4, 128.4, 128.5, 128.6, 138.8, 168.5.

***N*-(Trimethylsilyl)cinnamaldimine (2b)**:[21] ^1H NMR (300 MHz, $CDCl_3$) δ 0.12 (s, 9H), 6.86 (dd, J = 4.2, 1.8 Hz, 1H), 7.09 (d, J = 4.3 Hz, 1H), 7.26–7.40 (m, 3H), 7.43–7.62 (m, 2H), 8.68 (d, 1.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −1.0, 127.4, 128.7, 129.3, 135.4, 144.7, 170.3.

***N*-(Trimethylsilyl)benzophenoneimine (2c)**:[22] ^1H NMR (300 MHz, $CDCl_3$) δ 0.06 (s, 9H), 7.34–7.45 (m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 0.7, 127.9, 128.1, 128.2, 129.4, 141.6.

Synthesis of *N*-sulfonyl Imines 3a–f. A mixture of *N*-(trimethylsilyl) imine (10 mmol) and sulfonyl chloride (10 mmol) was heated at reflux in the appropriate anhydrous solvent (15 mL) or at 100 °C neat (see table) for 1 h under positive pressure of argon. No purification was necessary. Melting points of the *N*-(sulfonyl) imines were determined from samples recrystallized from ethyl acetate–hexane mixtures.

***N*-(Methanesulfonyl)benzaldimine (3a)**:[23] mp 89–91 °C, lit. mp 90–92 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 3.15 (s, 3H), 7.55 (t, J = 12 Hz, 2H), 7.68 (t, J = 12 Hz, 1H), 7.97 (d, J = 11 Hz, 2H), 9.04 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 40.3, 129.3, 131.3, 132.1, 135.2, 135.2, 171.7.

***N*-(*p*-Toluenesulfonyl)benzaldimine (3b)**:[11,12,16,23] mp 110 °C, lit. mp 108–109 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 2.44 (s, 3H), 7.35 (d, J = 8.3 Hz, 2H), 7.49 (t, J = 7.9 Hz, 2H), 7.63 (t, J

(19) Guillemin, J.-C.; Ammi, L.; Dennis, J.-M. *Tetrahedron Lett.* **1988**, *29*, 1287.
(20) Georg, G. I.; He, P.; Kant, J.; Wu, Z. *J. Org. Chem.* **1993**, *58*, 5771.
(21) Hart, D. J.; Ha, D.-C.; Yang, T. K. *J. Am. Chem. Soc.* **1984**, *106*, 4819.
(22) Kupfer, R.; Meier, S.; Würthwein, E.-U. *Synthesis* **1984**, 688.
(23) Davis, F. A.; Lamendola, J., Jr.; Nadir, U.; Kluger, E. W.; Sedergran, T. C.; Panunto, T. W.; Bilmers, R.; Jenkins, J., Jr.; Turchi, I. J.; Watson, W. H.; Chen, J. S.; Kimura, M. *J. Am. Chem. Soc.* **1980**, *102*, 2000.

= 6.5 Hz, 1H), 7.89–7.94 (m, 4H), 9.04 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.1, 128.5, 129.6, 130.2, 130.3, 131.7, 133.5, 135.4, 14.5, 170.6.

***N*-(Methanesulfonyl)cinnamaldimine (3c)**: mp 59–62 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 3.08 (s, 3H), 6.98 (d, J = 9 Hz, 1H), 7.02 (d, J = 9 Hz, 1H), 7.44–7.49 (m, 3H), 7.57–7.60 (m, 2H), 8.76 (d, J = 9.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 40.2, 124.2, 128.6, 129.1, 131.7, 133.9, 154.4, 172.2; FAB HRMS ($C_{10}H_{12}NO_2S$) *m/e* (M + 1) 210.0589, found 210.0605.

***N*-(*p*-Toluenesulfonyl)cinnamaldimine (3d)**:[12] mp 108–109 °C, lit. mp 109–110 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 2.42 (s, 3H), 6.94 (d, J = 9 Hz, 1H), 6.99 (d, J = 9 Hz, 1H), 7.29–7.57 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.7, 124.8, 128.0, 128.7, 129.2, 129.8, 131.7, 153.8, 170.9.

***N*-(Methanesulfonyl)benzophenone imine (3e)**:[24] mp 142 °C, lit. mp 141–142 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 3.19 (s, 3H), 7.38–780 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$, −40 °C) δ 42.9, 127.9, 128.4, 128.6, 130.8, 131.1, 133.7, 135.1, 136.9, 179.9.

***N*-(*p*-Toluenesulfonyl)benzophenone imine (3f)**:[12,25] mp 103 °C, lit. mp 101–102 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 2.42 (s, 3H), 7.28 (d, J = 9 Hz, 2H), 7.34–7.47 (m, 4H), 7.48–7.59 (m, 6H), 7.82 (d, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.5, 127.3, 128.0, 129.3, 138.4, 143.3, 178.7.

Acknowledgment. Financial support from the National Institutes of Health (RO1 CA 55160) is acknowledged. Support is also acknowledged from the Kansas Health Foundation and the Scientific Educational Partnership of Marion Merrell Dow for postdoctoral fellowships awarded to G. C. B. Harriman.

Supporting Information Available: ^1H and ^{13}C NMR spectra of the nonpurified *N*-sulfonyl imines (one-flask conversions of aldehydes or ketones to *N*-sulfonyl imines) (19 pages). This material is contained in libraries on microfiche, immediately following this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO950383X

(24) Bucciarelli, M.; Forni, A.; Moretti, I.; Torre, G. *J. Chem. Soc. Perkin Trans. 2* **1983**, 923.

(25) Dubina, V. L.; Burmistrov, S. I. *Zh. Org. Khim.* **1967**, *3*, 424. *Chem. Abstr.* **1967**, *66*, 55171z.