A Straightforward Route to Piloty's Acid Derivatives: A Class of Potential Nitroxyl-Generating Prodrugs

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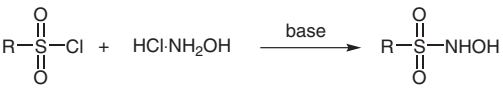
Abstract: A series of Piloty's acid derivatives were easily prepared under mild and neutral conditions. The ease of isolation of the final product offers a marked advantage over well-known procedures. This methodology is particularly attractive as it cleanly provided low molecular weight aliphatic sulfohydroxamic acids, which are very interesting for their tendency to generate HNO under physiological conditions.

Key words: Piloty's acid, NO, HNO, MgO, sulfohydroxamic acids

In the mid 1980's,[1] nitric oxide's (NO) reputation was unexpectedly elevated from that of harmful, polluting gas, which is formed when nitrogen burns in automobile exhaust fumes, to a molecule of potential biological relevance. In the past few years, NO has received intense attention in the life sciences and medicine. In this context, the biochemistry of nitroxyl[2] (HNO), the one-electron reduction product of NO, has attracted considerable interest as a new player in NO research for its remarkable biological activity which has been until now largely ignored.[3]

Nitroxyl is usually generated in solution[4] by Angeli's salt[5] ($Na_2N_2O_3$), a highly oxidizing compound that readily decomposes to form HNO via oxyhyponitrite anion $HN_2O_3^-$.[6] Another very interesting HNO donor is the benzenesulfohydroxamic acid, well known as Piloty's acid (PA).[7] Some recent studies[8] have highlighted that PA decomposes to HNO through a base-catalyzed deprotonation mechanism[9] or releases NO upon oxidation.[2e,7b,10] In 1998, Shoeman and Nagasawa[11] have also observed that methanesulfohydroxamic acid (MHSA), the simplest member of the aliphatic sulfohydroxamic acid series, was able to decompose to HNO at a rate comparable to Angeli's salt, and at physiological pH.[12]

Following this propensity of sulfohydroxamic acids to release nitroxyl, we have thought to prepare a library of Piloty's acid derivatives reacting a sulfonyl chloride (traditionally used to synthesize sulfonamide) with hydroxylamine hydrochloride in basic medium (Scheme 1).[13] Unfortunately, perusal of the literature[14] revealed that there are several important problems associated with this classical sulfonylation reaction (Scheme 1), which restrict its scope.[15] In fact, although the procedure is highly reactive and successful for the preparation of simple sulfonamides (using an amine instead of hydroxylamine), sulfohydroxamic acids are obtained in quite low yields after several complex purification steps.[16] Extensive studies on the synthesis of sulfonamides have revealed that sulfonylation of weakly nucleophilic amines (e.g. NH_2OH) is difficult; beside sulfonyl chlorides are highly reactive and often unstable species.[17]



R = alkyl, aryl

base = K_2CO_3, NaOEt, EtONa, Et_3N

Scheme 1 Classical approach to sulfohydroxamic acids

Moreover, sulfohydroxamic acids[18] having relatively short alkyl hydrocarbon (1–6 carbon) chains are water soluble and their purification by aqueous workup is elaborated and tedious. On the other hand, alternative methodology, based on the use of leaving groups other than chloride,[19] does not avoid all the drawbacks of the sulfonyl chlorides. In addition direct sulfonylation of hydroxylamine itself is well known to result in a mixture of N- and O-sulfonylated as well as di- and trisulfonylated products.[14b]

Therefore, the development of a facile method for the synthesis of 'sulfonamide bond', which takes place under mild and neutral conditions, is strongly desired. In recent years, mineral oxides have gained some attention because of reaction rate enhancement, selectivity, easier workup and the eco-friendly, green, reaction conditions.[20]

In this context, Rho et al.[21] have recently developed an efficient and chemoselective N-sulfonylation of amino alcohols in the presence of MgO.[22] The use of this metal oxide[23] becomes much more remarkable to overcome the most of the problems associated with the synthesis of sulfohydroxamic acids. Therefore, we chose to exploit the utility of MgO as base for the coupling of less reactive *N*-hydroxylamine with sulfonyl chlorides.

Initially, we chose 4-methylbenzensulfonyl chloride (**1a**) and hydroxylamine hydrochloride ($HCl·NH_2OH$), as the model substrates for optimization of the reaction conditions (Scheme 2). Hydroxylamine hydrochloride was initially deprotonated using one equivalent of MgO in methanol–water. In the absence of H_2O (required for a partial solubilization of $HCl·NH_2OH$ and MgO), the

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hydroxylamine reacts very slowly with the sulfonylating reagent and the yields are generally low. The sulfonyl chloride **1a**, dissolved in THF, and an additional equivalent of MgO were then added to the hydroxylamine solution and the resulting mixture was vigorously stirred at room temperature until the sulfonyl chloride has completely disappeared, as monitored by TLC. The reaction was complete in about 12 hours (Scheme 2).

After the completion of the reaction, the mixture was filtered first through a pad of Celite, and then on a short plug of silica gel. The clear filtrate was dried over $MgSO_4$ and evaporated to dryness to give the resulting *N*-hydroxysulfonamide **2a** (55%) as a crystalline solid. The purity, as checked by analytical RP-HPLC, was satisfactory (91%). All the spectroscopic analysis[24] clearly revealed that no traces of O-sulfonylated or N,O-bis-sulfonylated derivatives were present under the conditions employed.

In a second set of experiments, various conditions including solvent, bases, and reaction temperature were examined for this N-sulfonylation reaction (Table 1). Inferior results, both in terms of yield and purity of the target compound, were obtained when other solvents such as 1,2-dimethoxyethane (DME), 1,4-dioxane or CH_2Cl_2 were used. Other bases such as ZnO, CuO, $NaHCO_3$, NaOH (Schotten–Baumann conditions), TEA and pyridine were also tried in the reaction, but MgO was demonstrated to be the best choice. Although the sulfonylation reaction proceeded smoothly (in about 4 h) at a temperature higher then 40 °C, we observed the collapse of the yields of **2a** (23%) and an increasing of the side products due to the decomposition of the sulfonyl chloride. N,O-Bis-sulfonylated derivatives were observed as by-products too.

Afterward, further experiments were carried out using different combinations of equivalents of $HCl{\cdot}NH_2OH$ (from 1.0 to 3.0 equiv) and MgO (from 1.0 equiv to 3.0 equiv). We observed that two equivalents of hydroxylamine hydrochloride and three equivalents of magnesium oxide in a MeOH–H_2O–THF (3:2:30) solution efficiently promoted the sulfonylation reaction in only two hours at room temperature giving the desired sulfohydroxamic acid **2a** in 85% yield (purity >95%).

Encouraged by our initial studies, we then investigated the generality and versatility of this procedure using a series of structurally different sulfonyl chlorides (commercially available) under these optimized conditions. A combinatorial library (parallel format) of sulfohydroxamic acids was smoothly prepared in good to high yields and the results are summarized in Table 2.

The methodology is efficient and successful both with aromatic and with aliphatic sulfonic chloride although the yields are less satisfactory with the aliphatic substrates (R = aliphatic residue). Aromatic sulfohydroxamic acids containing various electron-donating and electron-withdrawing substituents were obtained in good to excellent yields (entries 1–6 and 7–9, Table 2). No remarkable electronic effects on the reaction were observed. No significant steric effects were observed for the *ortho*-, *meta*-, and *para*-substituted sulfonyl chloride (entries 4, 5 and 7–9, Table 2). The reaction is not only limited to hydroxylamine but works well also with N- and/or O-alkylated hydroxylamines (entries 9–11, Table 2). Moreover, when a ketone and sulfonyl chloride groups are present in the same substrate (**1o**, entry 15, Table 2), only the sulfonyl chloride moiety is selectively transformed to the corresponding *N*-hydroxyamide (**2o**, entry 15, Table 2).

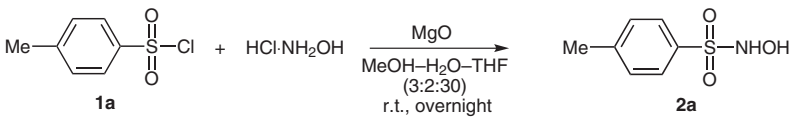
Table 1 Chemoselective Synthesis of **2a** under Various Reaction Conditions

Entry	Solvent	Base[a]	Time	Yield[b] (%)
1	Py	Py	12	18
2	CH_2Cl_2	TEA (2.0)	12	11
3	MeOH–H_2O (2:3)	K_2CO_3 (1.0)[14b]	12	24
4	MeOH–THF (3:2)	MgO (2.0)	12	5
5	MeOH–H_2O–THF (3:2:30)	MgO (2.0)	6	55
6	MeOH–H_2O–THF (3:2:30)	MgO (3.0)	2	85
7	MeOH–H_2O–THF (3:2:30)	MgO (5.0)	2	71
8	H_2O–DME (2:30)	MgO (3.0)	6	60
9	H_2O–1,4-dioxane (2:30)	MgO (3.0)	6	45
10	MeOH–H_2O–THF (3:2:30)	Ag_2O (3.0)	6	65
11	MeOH–H_2O–THF (3:2:30)	CuO (3.0)	6	53
12	MeOH–H_2O–THF (3:2:30)	ZnO (3.0)	6	47
13	MeOH–H_2O–THF (3:2:30)	$NaHCO_3$ (3.0)	12	16

[a] The molar equivalents are given in parentheses.
[b] Isolated yields.

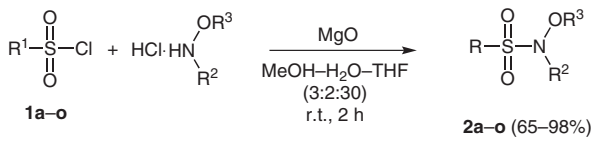
All the sulfonyl hydroxamates were fully characterized by NMR and ES-MS.[25] These results show that the majority of the synthesized compounds have purity higher than 95%. More importantly, no column purification was needed for the isolation of the product.

The reason for N-sulfonylation induced by metal oxide has not been entirely clarified; most probably the reaction mechanism is analogous to that observed in the selective N-acylation of amino alcohols.[22] It seems likely that the coordinating ability of magnesium ion[26] to the double

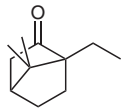


Scheme 2 Synthesis of *N*-hydroxy-4-methylbenzenesulfonamide

Table 2 Synthesis of Sulfohydroxamic Acids



1a–o **2a–o** (65–98%)

Entry	R^1	R^2	R^3	Product	Yield (%)
1	4-MeC_6H_4	H	H	**2a**	85%
2	2-MeC_6H_4	H	H	**2b**	74%
3	4-*t*-BuC_6H_4	H	H	**2c**	77%
4	2,4,6-(*i*-$Pr)_3C_6H_2$	H	H	**2d**	90%
5	2,6-$(MeO)_2C_6H_3$	H	H	**2e**	95%
6		H	H	**2f**	96%
7	2-$O_2NC_6H_4$	H	H	**2g**	97%
8	3-$O_2NC_6H_4$	H	H	**2h**	95%
9	4-$O_2NC_6H_4$	H	H	**2i**	97%
10	4-*t*-BuC_6H_4	Me	Me	**2j**	97%
11	4-MeC_6H_4	H	Bn	**2k**	95%
12	Me	H	H	**2l**	65%
13	Pr	H	H	**2m**	76%
14	Bu	H	H	**2n**	71%
15		H	H	**2o**	98%

bond of sulfonyl chloride activates the leaving ability of chloride playing a crucial role in the selective N-sulfonation of NH_2OH.[27] In the presence of MgO, only the more nucleophilic amino group is able to react with activated sulfonyl chloride.

In summary we have investigated the reactions of $HCl{\cdot}NH_2OH$ with structurally different sulfonyl chlorides in the presence of MgO and found that they can be chemoselectively converted to the corresponding *N*-sulfohydroxamic acids under neutral and mild conditions. The reaction does not require any aqueous workup, and *N*-sulfohydroxamic acids are isolated pure after a simple filtration. In comparison with other procedures, the use of MgO in the place of tertiary amine or other bases gives access to sulfohydroxamates more efficiently and in higher yields (65–98%). All the compounds obtained showed NMR and mass spectral data compatible with the assigned structures. No side reactions/products were observed during the course of the reaction. The technique described could be easily used in a parallel synthesis format. The whole protocol has potential use in the high throughput synthesis for this class of compounds.

Acknowledgment

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4-*tert*-Butyl-*N*-hydroxybenzenesulfonamide (2c): According to the procedure previously described for **2b**, the sulfohydroxamic acid **2c** was isolated as a white waxy solid in 77% yield (98% purity). ^{1}H NMR (DMSO): δ = 9.53 (s, 1 H), 7.52 (d, *J* = 8.5 Hz, 2 H), 7.32 (d, *J* = 8.4 Hz, 2 H), 1.24 (s, 9 H). ^{13}C NMR (DMSO): δ = 156.4, 134.7, 125.9, 125.5, 35.1, 31.3. HRMS (ESI): *m*/*z* [M + H$^+$] calcd for $C_{10}H_{16}NO_3S$: 230.0851; found: 230.0857. Anal. Calcd for $C_{10}H_{15}NO_3S$: C, 52.38; H, 6.59; N, 6.11. Found: C, 52.44; H, 6.39; N, 6.01.

***N*-Hydroxy-2,4,6-triisopropylbenzenesulfonamide (2d)**: According to the procedure previously described for **2b**, the sulfohydroxamic acid **2d** was isolated as a crystalline white solid in 90% yield (96% purity); mp 212–213 °C (dec.). ^{1}H NMR (DMSO): δ = 7.51 (br s, 2 H), 6.92 (s, 2 H), 4.53 (m, 2 H), 2.75 (m, 1 H), 1.13 (d, *J* = 6.9 Hz, 6 H), 1.07 (d, *J* = 6.8 Hz, 12 H). ^{13}C NMR (DMSO): δ = 147.4, 146.9, 141.8, 121.5, 33.4, 28.2, 24.9, 23.9. HRMS (ESI): *m*/*z* [M + H$^+$] calcd for $C_{15}H_{26}NO_3S$: 300.1633; found: 300.1626. Anal. Calcd for $C_{15}H_{25}NO_3S$: C, 60.17; H, 8.42; N, 4.68. Found: C, 60.23; H, 8.49; N, 4.45.

***N*-Hydroxy-2,6-dimethoxybenzenesulfonamide (2e)**: According to the procedure previously described for **2b**, the sulfohydroxamic acid **2e** was isolated as a crystalline white solid in 95% yield (97% purity); mp 158–160 °C. ^{1}H NMR (DMSO): δ = 8.59 (d, *J* = 3.5 Hz, 1 H), 7.96 (d, *J* = 3.5 Hz, 1 H), 6.82 (d, *J* = 8.7 Hz, 1 H), 5.83 (m, 2 H), 3.02 (d, *J* = 6.6 Hz, 6 H). ^{13}C NMR (DMSO): δ = 164.8, 158.3, 132.9, 116.4, 105.2, 56.2, 55.8. HRMS (ESI): *m*/*z* [M + H$^+$] calcd for $C_8H_{12}NO_5S$: 234.0436; found: 234.0430. Anal. Calcd for $C_8H_{11}NO_5S$: C, 41.20; H, 4.75; N, 6.01. Found: C, 41.31; H, 4.70; N, 6.12.

***N*-Hydroxythiophene-2-sulfonamide (2f)**: According to the procedure previously described for **2b**, the sulfohydroxamic acid **2f** was isolated as a waxy solid in 96% yield (97% purity). ^{1}H NMR ($CDCl_3$): δ = 7.75 (m, 1 H), 7.71 (m, 1 H), 7.35 (br s, 2 H), 7.16 (m, 1 H). ^{13}C NMR ($CDCl_3$): δ = 134.5, 133.9, 127.5, 116.5. HRMS (ESI): *m*/*z* [M + H$^+$] calcd for $C_4H_6NO_3S_2$: 179.9789; found: 179.9793. Anal. Calcd for $C_4H_5NO_3S_2$: C, 26.81; H, 2.81; N, 7.82. Found: C, 26.74; H, 2.90; N, 7.74.

***N*-Hydroxy-2-nitrobenzenesulfonamide (2g)**: According to the procedure previously described for **2a**, the sulfohydroxamic acid **2g** was isolated as a crystalline yellow solid in 97% yield (99% purity); mp 154–157 °C. ^{1}H NMR (DMSO): δ = 7.83 (d, *J* = 7.8 Hz, 1 H), 7.55 (m, 3 H).

^{13}C NMR (DMSO): δ = 130.7, 130.0, 129.1, 122.4. HRMS (ESI): *m*/*z* [M + H$^+$] calcd for $C_6H_7N_2O_5S$: 219.0076; found: 219.0065. Anal. Calcd for $C_6H_6N_2O_5S$: C, 33.03; H, 2.77; N, 12.84. Found: C, 32.91; H, 2.81; N, 12.92.

4-*tert*-Butyl-*N*-methoxy-*N*-methylbenezenesulfonamide (2j): According to the procedure previously described for **2b**, the sulfohydroxamic acid **2j** was isolated as a crystalline white solid in 97% yield (99% purity); mp 112–114 °C. ^{1}H NMR ($CDCl_3$): δ = 7.80 (d, *J* = 8.3 Hz, 2 H), 7.57 (d, *J* = 8.3 Hz, 2 H), 3.82 (s, 3 H), 2.79 (s, 3 H), 1.36 (s, 9 H). ^{13}C NMR ($CDCl_3$): δ = 157.6, 129.5, 129.2, 125.8, 63.7, 39.2, 35.2, 31.0. HRMS (ESI): *m*/*z* calcd for $C_{12}H_{19}NO_3S$: 257.1086; found: 257.1081. Anal. Calcd for $C_{12}H_{19}NO_3S$: C, 56.01; H, 7.44; N, 5.44. Found: C, 55.89; H, 7.48; N, 5.37.

(7,7-Dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl)-*N*-hydroxymethanesulfonamide (2o): According to the procedure previously described for **2b**, the sulfohydroxamic acid **2o** was isolated as a crystalline white solid in 98% yield (98% purity); mp 122–124 °C; $[\alpha]^{20}_D$ +27.89 (*c* = 0.384, MeOH). ^{1}H NMR (DMSO): δ = 9.65 (s, 1 H), 9.05 (s, 1 H), 2.96 (d, *J* = 14.8 Hz, 1 H), 2.49 (m, 1 H), 2.32 (m, 2 H), 2.05 (t, *J* = 4.7 Hz, 1 H), 1.92 (m, 2 H), 1.43 (m, 2 H), 1.02 (s, 3 H), 0.80 (s, 3 H). ^{13}C NMR (DMSO): δ = 185.76, 176.39, 59.40, 49.44, 45.45, 43.07, 42.75, 26.99, 26.88, 19.88, 19.3. HRMS (ESI): *m*/*z* calcd for $C_{10}H_{17}NO_4$: 247.0878; found: 247.0871. Anal. Calcd for $C_{10}H_{17}NO_4S$: C, 48.57; H, 6.93; N, 5.66. Found: C, 48.52; H, 6.87; N, 5.71.

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