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Site-Selective Methylation of N^{β}-Nosyl Hydrazides of *N*-Nosyl Protected α-Amino Acids

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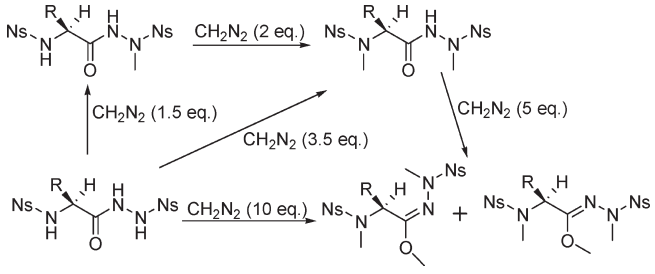

The methylation reaction of N^{β}-nosyl hydrazides of *N*-nosyl protected α-amino acids by using diazomethane shows a controlled regiochemical trend and makes it possible to obtain the corresponding products methylated at specific positions depending on the amount of diazomethane used. The observed selectivity is closely connected with the different acidity of sulfonyl hydrazide, sulfonamide, and acyl hydrazine protons present in the analyzed substrates. The reactivity order of these three diverse reactive sites is supported by theoretical calculations. The hydrazine derivatives considered in this work belong to a class of compounds with interesting biological activity and of great interest in organic synthesis.

Introduction

Hydrazine derivatives are useful reaction intermediates in organic synthesis.[1] Furthermore, some biologically active molecules or intermediates involved in their synthesis are characterized by the presence of the hydrazine functional group.[2]

N-Alkyl-*N*,*N*′-bis(arylsulfonyl)hydrazines display significant antineoplastic activity against a variety of tumor cells.[3] Their tumor-inhibitory properties can be attributed to their capacity to generate, under physiological conditions, alkylating species that act by modifying directly the DNA.[4]

Acyl hydrazine substrates substituted on the β nitrogen atom with an arenesulfonyl leaving group are of great interest also in organic chemistry.[5] Oxidizing agents convert *N*-acyl-*N*′-(arylsulfonyl)hydrazines to the corresponding acyl radicals,[6] which are useful reaction intermediates in carbon−carbon bond formation and in particular in the synthesis of carbocycles.[7]

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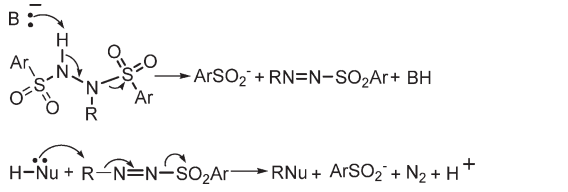

FIGURE 1. Formation of diimide intermediates from *N*-alkyl-*N*,*N*′-bis(arylsulfonyl)hydrazines.

Generally, the activity of these hydrazine derivatives takes place through the generation of a reactive diimide intermediate.[3−6] The formation and the nature of this species determine the biological activity of the *N*-alkyl-*N*,*N*′-bis(arylsulfonyl)hydrazine derivatives and the chemical reactivity of *N*-acyl-*N*′-(arylsulfonyl)hydrazines. In the first case, the diimide intermediate formation depends on the acidity of the hydrazide proton and the leaving group ability of the arenesulfinate ion ($ArSO_2^-$) (Figure 1).[3] After nucleophilic attack on the alkyl group, the diimide intermediate decomposes with loss of a molecule of nitrogen and expulsion of the second arenesulfinate ion and gives rise to the alkylated nucleophile (Figure 1). The presence of the alkyl substituent is essential for the generation of reactive species involved in the antineoplastic activity. In fact *N*,*N*′-bis(arylsulfonyl)-hydrazines not alkylated on the hydrazine moiety do not show antitumor properties.[3a]

The evolution of the *N*-acyl-*N*′-(arylsulfonyl)hydrazine systems is also associated with the formation of diimide species. The anion resulting from the removal of the sulfonamide proton, undergoes a 1,2-hydride shift, expulsion of sulfinate ion, and migration of an electron pair to form the N=N double bond.[5b] The acyl diimide thus obtained decomposes spontaneously into the corresponding aldehyde.[5] This reaction represents an alternative to the use of hydride reducing agents in the conversion of carboxylic acid derivatives to aldehydes; differently, the acyl alkyl diimides tautomerize readily to the corresponding hydrazones.[8] Furthermore, an acyl diimide derivative is also involved in the formation of the acyl radical that is the key intermediate responsible for the antitubercolar activity of isoniazid.[9]

Several unalkylated *N*-acyl-*N*′-(arylsulfonyl)hydrazines show inhibitory activity against a series of serine proteases involved in the pathogenesis or in the control of some human diseases. In particular, a series of *N*-acyl-*N*′-(arylsulfonyl) substituted cyclic hydrazide derivatives are selective inhibitors of dipeptidyl peptidase IV.[10] Furthermore, tripeptides containing a C-terminal sulfonyl hydrazide functionality[11] have proven to be potent and selective inhibitors of a serine protease that is essential for the replication of the hepatitis C virus[12] and involved in viral persistence in organisms.

Also, many types of sulfonamide compounds show biological activity[13] and are widely used in therapy as antibacterial,[14] hypoglycemic,[15] diuretic,[16,17] anticarbonic anhydrase,[16,18] and antithyroid[19] drugs.

Results and Discussion

With the aim to obtain new and potentially active substrates we have undertaken the synthesis of molecules having both sulfonyl and sulfonamide functionalities.

For this purpose, the N^{β}-4-nitrobenzenesulfonyl hydrazides (N^{β}-nosyl hydrazides) of *N*-nosyl protected α-amino acids were chosen as starting model systems. The selective alkylation of these substrates was performed using diazomethane as methylating agent,[20] exploiting the different acidity of sulfonamide and amide protons.[21]

Diazomethane acts as a base and removes an acidic proton of the reacting molecule. The methyl diazonium ion obtained is capable of alkylating the nucleophile species generated from the initial acid−base reaction.[22]

As reported in the literature, the acidity in DMSO of both sulfonamide and sulfonyl hydrazide protons is higher than that of the acyl hydrazine protons (pK_a $PhSO_2NH_2$ = 16.1; pK_a $PhSO_2NH_2NH_2$ = 17.1; pK_a $PhCONH_2NH_2$ = 18.9);[21] instead, the pK_a values, measured in DMSO, of sulfonamides and sulfonyl hydrazides are rather similar.[21]

These data suggest that the protons of the sulfonamide and sulfonyl hydrazide functions present in the same molecule of the *N*′-(*N*-nosyl-α-aminoacyl)-*N*″-nosyl hydrazines could have comparable acidity, with both more acidic than the acyl hydrazine proton.

With the aim to estimate the acidic properties of this kind of compounds, density functional theory (DFT) computations have been performed on the synthesized species. The gas-phase acidities were calculated following the procedure described in the Experimental Section.

The three considered anionic forms, named An($\mathbf{N_a}$), An($\mathbf{N_b}$), and An($\mathbf{N_c}$) with regard to the amino groups of different nature present in the **3a** molecule, are shown in Figure 2.

From these calculations it is evident that the An($\mathbf{N_a}$) anionic species ($\Delta\Delta H$ = 0.0 kcal/mol) is the most stable one followed by An($\mathbf{N_b}$) ($\Delta\Delta H$ = 12.4 kcal/mol) and An($\mathbf{N_c}$) ($\Delta\Delta H$ = 14.1 kcal/mol), respectively, hence with regard to acidic properties of the three sites in the **3a** molecule, we propose the acidity order of $\mathbf{N_a} > \mathbf{N_b} > \mathbf{N_c}$.

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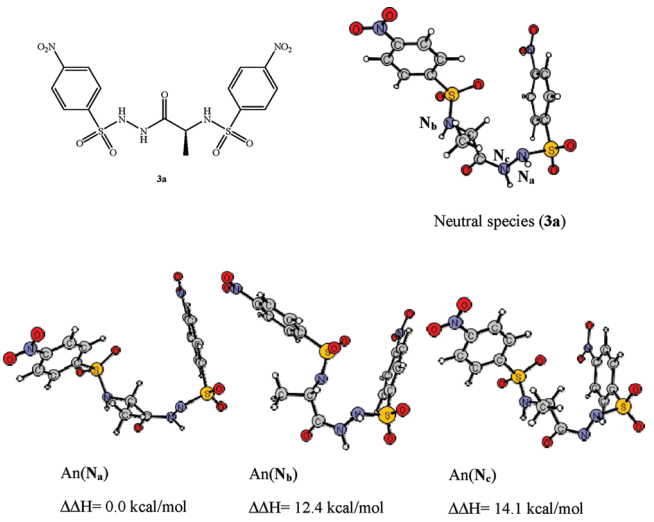

FIGURE 2. B3LYP optimized structures of the **3a** neutral molecule and its related anionic forms An($\mathbf{N_a}$), An($\mathbf{N_b}$), and An($\mathbf{N_c}$).

These theoretical findings also quantify the different acidic nature of the sulfonamide and sulfonyl hydrazide protons.

On the basis of these predictions, we were interested in using the diazomethane as probe molecule to test the acidity of the $\mathbf{N_a}$, $\mathbf{N_b}$ and $\mathbf{N_c}$ protons of the hydrazine substrates. The subsequent formation of the alkylation products, resulting from the reaction of the generated nucleophilic sites with the methyl diazonium ion, represents a measure of the base activity of diazomethane, depending on the acidity of the $\mathbf{N_a}$, $\mathbf{N_b}$, and $\mathbf{N_c}$ protons.

The nosyl-substituted acyl hydrazines **3a**−**c** were easily prepared by treatment of nosylhydrazide (**2**)[23] with the appropriate *N*-nosyl-α-aminoacyl chloride **1a**−**c**[20b,c] (Scheme 1, Table 1).

SCHEME 1. Synthesis of Hydrazines 3a−c

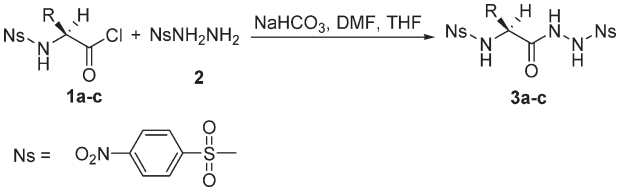

TABLE 1. Synthesis of Hydrazines 3a−c

compound	R	yield (%)
3a	CH_3	80
3b	$CH_2CH(CH_3)_2$	73
3c	CH_2Ph	70

The *N*′-(*N*-nosyl-L-alanyl)-*N*″-nosylhydrazine (**3a**), chosen as model system, was dissolved in dry THF and treated with 1.5 equiv of a 0.66 M methylene chloride solution of diazomethane[24] at room temperature. After 50 min, evaporation of the solvent under vacuum afforded *N*′-(*N*-nosyl-L-alanyl)-*N*″-methyl-*N*″-nosylhydrazine (**4a**) in quantitative yield (Scheme 2, Table 2).

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SCHEME 2. Synthesis of Hydrazines 4a−c

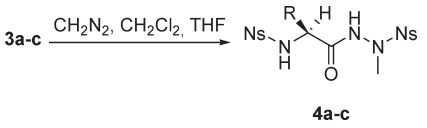

TABLE 2. Synthesis of Hydrazines 4a−c

compound	R
4a	CH_3
4b	$CH_2CH(CH_3)_2$
4c	CH_2Ph

Treatment of the hydrazines **3b,c** (Scheme 2) under the same conditions as **3a** led to the formation of the corresponding derivatives **4b,c**, selectively methylated on the sulfonyl hydrazide function. In all cases, the products were recovered in quantitative yields and high purity without need of chromatographic separation. The methylation reaction is chemospecific for the alkylation of the sulfonyl hydrazide function. Both small (1 mmol, 0.55 g of **3c**) and larger scale (14 mmol, 8.0 g of **3c**) reactions were performed successfully and with safety.

To investigate the behavior of its acidic protons, B3LYP calculations were carried out also on **4a** species and its anionic forms. The optimized structures are depicted in Figure 3.

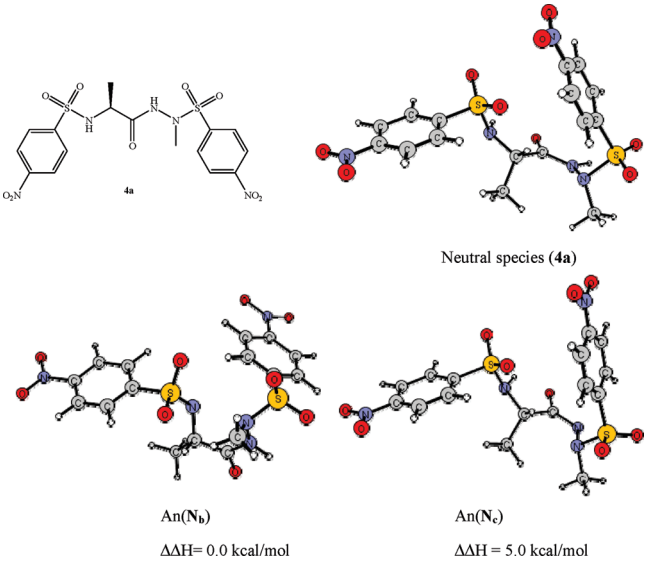

FIGURE 3. B3LYP-optimized structures of the **4a** neutral molecule and its two related anionic forms An($\mathbf{N_b}$) and An($\mathbf{N_c}$).

Also in this case, the acidities of $\mathbf{N_b}$ and $\mathbf{N_c}$ were calculated and showed the same trend as the **3a** species (see Figures 2 and 3). In particular the anion having the negative charge on the $\mathbf{N_b}$ site results more stable than that having the negative charge on the $\mathbf{N_c}$ one, by about 5 kcal/mol.

The theoretical acidity order proposed for the monomethylated substrate **4a** was confirmed by experimental data. In fact, the treatment of hydrazines **4a**−**c** with 2 equiv of a 0.66 M methylene chloride solution of diazomethane at room temperature led to the formation of the corresponding

SCHEME 3. Synthesis of Hydrazines 5a−c

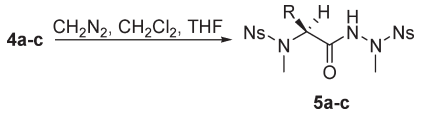

TABLE 3. Synthesis of Hydrazines 5a−c

compound	R
5a	CH_3
5b	$CH_2CH(CH_3)_2$
5c	CH_2Ph

dimethylated products **5a−c** (Scheme 3), which are recovered in quantitative yields and high purity without need of chromatographic separation (Table 3). The methodology was expanded to the large-scale synthesis (gram quantity).

Furthermore, in an additional experiment, the hydrazines **5a−c** were completely methylated by treating them with 5 equiv of a 0.66 M methylene chloride solution of diazomethane at room temperature (Scheme 4). The ^{1}H NMR spectrum of each crude reaction product, obtained after evaporation of the solvent under vacuum, indicated the presence of resonance signals corresponding to a mixture of the two isomers **6a−c** and **7a−c** in an approximately 1:3 ratio, respectively (Scheme 4).

SCHEME 4. Synthesis of Trimethylated Compounds 6a−c and 7a−c

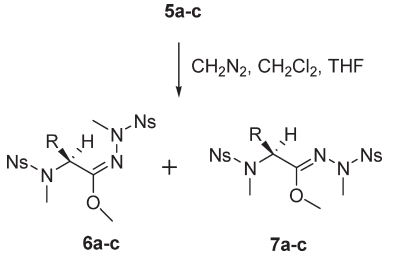

TABLE 4. Synthesis of Trimethylated Products 6a−c and 7a−c

	R	**6** yield (%)	**7** yield (%)
a	CH_3	21	60
b	$CH_2CH(CH_3)_2$	24	72
c	CH_2Ph	27	77

Chromatographic separation gave the trimethylated products **6a−c** and **7a−c** in 21−27% and 60−77% yield, respectively (Table 4). The methylation reaction was also performed successfully on a larger scale than 1 mmol. The formation of these compounds definitely confirms a chemospecific control of the methylation reaction of the sulfonyl hydrazide substrates by using diazomethane.

The hydrazines **3a−c** were then subjected to the reaction with different ratios of diazomethane: the treatment with 3.5 equiv of a 0.66 M methylene chloride solution of diazomethane afforded the corresponding dimethylated derivatives **5a−c**. Also in this case, the methylation reaction shows chemospecificity, providing the corresponding products methylated on the nitrogen atoms directly bound to the nosyl groups.

The same trimethylated products **6a−c** and **7a−c**, obtained from **5a−c** under the conditions previously described, were also obtained by treatment of the hydrazines **3a−c** with a large excess of diazomethane (10 equiv) for 5 h at room temperature. Therefore, the theoretical acidity order proposed above agrees well with the observed reactivity of the **3a** species with different stoichiometric ratios of diazomethane. Similar reasons can be advanced to account for the formation of the **5a** molecule starting from the **3a** one when an increased amount of diazomethane was considered.

TABLE 5. NBO Charges in |e| for 3a and 5a Species and Their Anionic Forms

	N_a	N_b	N_c	O
		3a		
neutral species	−0.684	−0.904	−0.475	−0.619
An(Na)	−0.806	−0.914	−0.440	−0.708
An(Nb)	−0.716	−0.920	−0.542	−0.736
An(Nc)	−0.663	−1.007	−0.489	−0.636
		5a		
neutral species			−0.476	−0.627
An(Nc)			−0.541	−0.740

A further increase of the quantity of diazomethane added to the **3a** species yielded the **6a** and **7a** trimethylated products. These species show the peculiarity to have the third methyl group introduced on the carbonyl oxygen atom rather than on the $\mathbf{N_c}$ site. In this case the acidic properties do not represent the only factor to explain the results, but the charge distribution can contribute to rationalize the experimental evidence. For this purpose an NBO analysis on the anionic forms of the **3a** species was performed, and the obtained net charge values of the acidic sites and the carbonyl oxygen present in the **3a** species are collected in Table 5. At first glance on this table, it is possible to deduce that the $\mathbf{N_c}$ site is still the less favored one in the methylation process because its charge value is the least negative with respect to the other considered sites. These results support the presence of the O-methylated products in the course of the synthetic process. In fact the An($\mathbf{N_c}$) species shows an NBO charge value on the carbonyl oxygen (−0.636 e) of about 0.147 e more negative than that found in the $\mathbf{N_c}$ deprotonated site (−0.489 e).

The NBO charges calculations were also extended to the **5a** neutral species and its relative anion and the obtained results are collected in Table 5. In the anionic species derived from **5a**, the charge value on the carbonyl oxygen (−0.740 e) is more negative than that present on the $\mathbf{N_c}$ site (−0.541 e, Table 5). These reasons can be advanced to explain the lack of the trimethylated form, having the third methyl group on the $\mathbf{N_c}$ position, as a possible product during the synthesis described in the present work.

Conclusions

The described methylation procedure of the N^{β}-nosyl hydrazides of the *N*-nosyl protected α-amino acids with diazomethane provides in high yields and purity the corresponding products selectively methylated at specific positions. The theoretical calculation of the acidity in the gas phase of some representative derivatives of the synthesized compounds is useful in the rationalization of the peculiar behavior shown by the hydrazine derivatives in the methylation reaction using different stoichiometric ratios of diazomethane. The different acidity of the three different reactive

sites present in the analyzed molecules determines the selectivity of the methylation reaction; this reaction is controlled by the formation of the more stable conjugated base. In any case, the formation of the methylated products in the reaction of used substrates with diazomethane follows the acidity trend of the NH groups. The observed selective O-methylation, during the treatment of the substrates **3a**−**c** and **5a**−**c** with diazomethane, could be justified by a hard−hard interaction driven by the charges present on the methyldiazonium ion and the oxygen atom of the anion derived from the deprotonation of the dimethylated compounds.

Experimental Section

Synthesis of *N′*-(*N*-Nosyl-α-aminoacyl)-*N″*-nosyl Hydrazines 3a−c. General Procedure. Sodium bicarbonate (10 mmol) and *N*,*N*-dimethylformamide (0.53 mmol) were added to a stirred solution of 4-nitrobenzenesulfonylhydrazide (**1**, 1 mmol) in dry tetrahydrofuran (10 mL); a solution of the appropriate *N*-nosyl-α-aminoacyl chloride[20b,c] (1 mmol) in dry tetrahydrofuran (10 mL) was then added, and the resulting mixture was stirred at room temperature for 60−90 min, until TLC analysis (chloroform/ethyl acetate 70:30 v/v) of the reaction mixture showed complete conversion of the precursor. Distilled water (15 mL) was added to the reaction mixture, and the solution was extracted with chloroform (3 × 10 mL). The combined organic extracts were washed once with 10% aqueous hydrochloric acid (10 mL) and once with brine (10 mL) and then dried over Na_2SO_4. The solvent was evaporated under vacuum to provide the corresponding nosyl-substituted acyl hydrazine **3a**−**c** in 70−80% yields.

***N′*-(*N*-Nosyl-L-alanyl)-*N″*-nosylhydrazine (3a).** Obtained as a pale yellow oil (80%); ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.40 (d, J = 2.4 Hz, 1H), 10.30 (d, J = 2.4 Hz, 1H), 8.50 (d, J = 8.4, 1H), 8.47−8.39 (m, 4H), 8.12−7.98 (m, 4H), 3.97−3.81 (m, 1H),1.02 (d, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 169.8, 150.7, 150.3, 144.6, 144.3, 130.1, 129.0, 125.2, 125.0, 52.6, 15.5. Anal. Calcd for $C_{15}H_{15}N_5O_9S_2$: C, 38.05; H, 3.19; N, 14.79. Found: C, 38.19; H, 3.18; N, 14.74.

Synthesis of *N′*-(*N*-Nosyl-α-aminoacyl)-*N″*-methyl-*N″*-nosyl Hydrazines 4a−c. General procedure. A 0.66 M methylene chloride solution of diazomethane (1.5 mmol) was added dropwise to a stirred solution of the appropriate *N′*-(*N*-nosyl-α-aminoacyl)-*N″*-nosyl hydrazine **3a**−**c** (1 mmol) in dry tetrahydrofuran at room temperature. The mixture was maintained under stirring for about 40−50 min, until TLC analysis (chloroform/ethyl acetate 60:40 v/v) of the reaction mixture showed complete conversion of the precursor. Evaporation of the solvent under vacuum provided the respective *N′*-(*N*-nosyl-α-aminoacyl)-*N″*-methyl-*N″*-nosyl hydrazine **4a**−**c** in quantitative yield. The methylation reaction was also performed successfully starting from 14 mmol (8.0 g) of the hydrazine **3c**.

***N′*-(*N*-Nosyl-L-alanyl)-*N″*-methyl-*N″*-nosylhydrazine (4a).** Obtained as a pale yellow oil (quantitative yield); ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.33 (s, 1H), 8.57 (d, J = 8.4 Hz, 1H), 8.41−8.32 (m, 4H), 8.04−7.92 (m, 4H), 3.85−3.73 (m, 1H), 2.89 (s, 3H), 1.05 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 170.3, 150.3, 149.7, 146.8, 142.0, 129.8, 128.1, 124.6, 124.5, 50.3, 38.0, 18.9. Anal. Calcd for $C_{16}H_{17}N_5O_9S_2$: C, 39.42; H, 3.52; N, 14.37. Found: C, 39.55; H, 3.50; N, 14.32.

Synthesis of *N′*-(*N*-Methyl-*N*-nosyl-α-aminoacyl)-*N″*-methyl-*N″*-nosyl Hydrazines 5a−c. General procedure. A 0.66 M methylene chloride solution of diazomethane (2 mmol) was added dropwise to a stirred solution of the appropriate *N′*-(*N*-nosyl-α-aminoacyl)-*N″*-methyl-*N″*-nosyl hydrazine **4a**−**c** (1 mmol) in dry tetrahydrofuran at room temperature. The mixture was maintained under stirring for about 60−70 min, until TLC analysis (chloroform/ethyl acetate 60:40 v/v) of the reaction mixture showed complete conversion of the precursor. Evaporation of the solvent under vacuum provided the respective *N′*-(*N*-methyl-*N*-nosyl-α-aminoacyl)-*N″*-methyl-*N″*-nosyl hydrazine **5a**−**c** in quantitative yield. The methylation reaction was also performed successfully starting from 13 mmol (7.5 g) of the hydrazine **4c**.

***N′*-(*N*-Methyl-*N*-nosyl-L-alanyl)-*N″*-methyl-*N″*-nosylhydrazine (5a).** Obtained as a pale yellow oil (quantitative yield); ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.35 (s, 1H), 8.48−8.38 (m, 4H), 8.01 (d, J = 9.0 Hz, 4H), 4.49 (q, J = 7.1 Hz, 1H),2.98 (s, 3H), 2.80 (s, 3H), 1.12 (d, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 169.8, 155.0, 150.7, 149.9, 144.0, 130.2, 128.9, 125.2, 124.9, 53.3, 38.47, 30.7, 15.5. Anal. Calcd for $C_{17}H_{19}N_5O_9S_2$: C, 40.71; H, 3.82; N, 13.97. Found: C, 40.69; H, 3.80; N, 14.04.

Treatment of *N′*-(*N*-Methyl-*N*-nosyl-α-aminoacyl)-*N″*-methyl-*N″*-nosyl Hydrazines 5a−c with Diazomethane. A 0.66 M methylene chloride solution of diazomethane (5 mmol) was added dropwise to a stirred solution of the appropriate *N′*-(*N*-methyl-*N*-nosyl-α-aminoacyl)-*N″*-methyl-*N″*-nosyl hydrazine **5a**−**c** (1 mmol) in dry tetrahydrofuran at room temperature. The mixture was maintained under stirring for about 80−90 min, until TLC analysis (diethyl ether/petroleum ether 70:30 v/v) of the reaction mixture showed complete conversion of the precursor. The organic solvent was removed under vacuum, and the oily residue was subjected to chromatography to provide compounds **6a**−**c** in 21−27% yields and compounds **7a**−**c** in 60−77% yields.

Chromatographic purification of the crude reaction product obtained by the reaction performed starting from 5 mmol (3.0 g) of **5c** afforded the corresponding trimethylated products **6c** (0.64 g) and **7c** (2.2 g) in 22% and 75% yields, respectively.

***(E)*-Methyl *N*-Methyl-*N*-nosyl-2-(*N*-methyl-4-nitrophenylsulfonamido)propanhydrazinoate (6a).** Obtained as a pale yellow oil (21%); ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.30 (d, J = 8.7 Hz, 4 H), 7.83 (d, J = 8.7 Hz, 4 H), 5.45 (q, J = 7.4 Hz, 1H), 3.50 (s, 3H), 2.92 (s, 3H), 2.74 (s, 3H), 1.32 (d, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 175.1, 166.0, 151.5, 150.0, 143.4, 132.7, 128.9, 125.3, 124.2, 56.4, 44.8, 38.5, 31.1, 15.7. Anal. Calcd for $C_{18}H_{21}N_5O_9S_2$: C, 41.94; H, 4.11; N, 13.59. Found: C, 42.09; H, 4.09; N, 13.53.

***(Z)*-Methyl *N*-Methyl-*N*-nosyl-2-(*N*-methyl-4-nitrophenylsulfonamido)propanhydrazinoate (7a).** Obtained as a pale yellow oil (60%); ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.40−8.52 (m, 4H), 8.17−8.00 (m, 4H), 5.12 (q, J = 6.7 Hz, 1H), 4.04 (s, 3H), 2.74 (s, 3H), 2.71 (s, 3H), 1.03 (d, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 161.2, 152.4, 148.7, 148.1, 143.2, 129.9, 128.1, 125.1, 123.3, 56.3, 51.5, 38.3, 30.9, 16.1 Anal. Calcd for $C_{18}H_{21}N_5O_9S_2$: C, 41.94; H, 4.11; N, 13.59. Found: C, 41.89; H, 4.12; N, 13.56.

Computational Details. Density Functional Theory calculations were performed on the **3a** and **4a** compounds and their relative neutral and anionic forms. The hybrid Becke three parameter exchange and Lee Yang and Parr correlation (B3LYP)[25,26] functional was used in both geometry optimization and frequency calculations as implemented in the Gaussian03 code.[27] All the calculations were carried out using the extended 6-311+G(2df,2p) basis set on all atoms.

Vibrational frequency calculations performed to determine the nature of stationary point of all the investigated species and to take into account the zero-point frequencies and the enthalpy terms. This approach proved to be adequate to describe with

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reasonable accuracy both the gas-phase acidities and basicities of a wide variety of molecular systems.[28−33]

In this work the enthalpy variation for the deprotonation process ($\Delta_{ac}H$) at 298 K of the neutral compound AH

$$AH \rightleftarrows A^- + H^+ \quad (1)$$

is used as acidity of the AH neutral species in the gas phase and can be calculated as follows:

$$\Delta_{ac}H = \Delta E^{\circ}_{elec} + \Delta ZPE + \Delta E^{298}{}_{vib} + \frac{5}{2}RT \quad (2)$$

where ΔE°_{elec}, ΔZPE, and $\Delta E^{298}{}_{vib}$ refer to the differences between the electronic energies at 0 K, the ZPE, and the thermal vibrational corrections of AH and A^-, respectively. The term $5/2RT$, necessary to convert the energy in enthalpy, includes the PV work term and the differences between the translational and rotational energy contributions of the species involved in the deprotonation process. The relative acidity values ($\Delta\Delta_{ac}H$) were computed as differences between the value of the more acidic compound and the given ones.

Natural bond orbital (NBO) analysis[34] was performed on all the neutral and charged species.

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Supporting Information Available: Complete list of authors for ref 27. Characterization of compounds **3b,c**, **4b,c**, **5b,c**, **6b,c**, and **7b,c**. ^{1}H NMR and ^{13}C NMR spectra of compounds **3a−c**, **4a−c**, **5a−c**, **6a−c**, and **7a−c**. Tables of atom coordinates and absolute energies. This material is available free of charge via the Internet at http://pubs.acs.org.

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