Nitrosation of Hindered Amides

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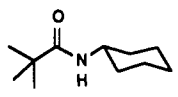
N-Nitrosoamides are among the most widely used synthetic intermediates for the preparation of diazo alkanes, generation of aryl radicals, and deamination of aliphatic amines.[1] More recently, the enhanced reactivity of nitrosoamides and nitroamides with a variety of nucleophiles was utilized for the conversion of RCONHR′ into RCONHR″, $RCON_3$, and RCOSR″,[2] and for the cleavage of certain peptide amide bonds[3] under mild conditions. In general agreement with the literature,[4,5] we found[2,3a,6] that N_2O_4/NaAcO was an excellent reagent for the nitrosation of amides in cold CH_2Cl_2. Nevertheless, under such conditions several hindered peptide bonds could not be nitrosated.[3a]

In this paper we report the reaction of three nitrosating agents on compounds containing sterically hindered amide bonds: *N*-cyclohexyl-2,2-dimethylpropanamide (**1**), *N*-acetyl-L-valine methyl ester (Ac-Val-OMe, **2**) and *N*-acetyl-L-isoleucine methyl ester (Ac-Ile-OMe, **3**). The most promising nitrosating reagents have been then applied to *N*-benzyloxycarbonyl-L-isoleucyl-L-valine methyl ester (Z-Ile-Val-OMe, **4**) and *N*-benzyloxycarbonyl-L-valyl-L-leucine methyl ester (Z-Val-Leu-OMe, **5**).



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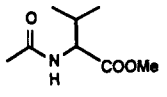

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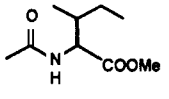

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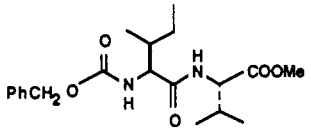

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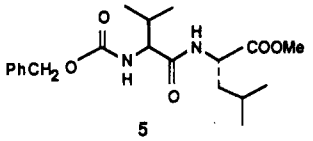

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When N_2O_4/NaAcO was used, compounds **1–3** gave no detectable amounts of N-nitrosated products.[3a] Substitution of pyridine (py) for NaAcO, which we had shown to improve the nitrosation yields of some moderately hindered peptide bonds,[7] did not afford any significant improvement in the cases studied here (**1–3**). After several trials (changing the base, adding either Me_2S or EtSH in different amounts), encouraging yields were attained when 10 equiv of Me_2S was added to a solution of the amide in py/CH_2Cl_2 (60% of nitrosation in the case of **2** and 30% in **3**, but 0% in **1**).

It is known that, upon the oxidation of organic sulfides, selenides, phosphines, etc., with nitronium ions,[8] equilibria such as shown in eq 1 can be reached under appropriate conditions. Thus, the nitrosating power against $PhNMe_2$ shown by mixtures of R_2S, R_2Se, R_3P, etc., with NO_2BF_4 or NO_2PF_6 has been attributed either to the *S*-nitrito (*Se*-nitrito, *P*-nitrito, etc.) species or to NO^+.[8]

$$R_2S + NO_2^+ \rightleftharpoons R_2S^+\text{–}NO_2 \rightleftharpoons R_2S^+\text{–}O\text{–}N{=}O \rightleftharpoons R_2S{=}O + NO^+ \quad (1)$$

These results encouraged us to investigate the nitrosation of **1–3** with NO_2BF_4 in the presence of a sulfide or sulfide-like compound and a base, according to the hypothetical reaction shown in eq 2. After confirmation of

$$RCONHR + NO_2^+ + R_2S + \text{base} \rightarrow RCON(NO)R + R_2S{=}O + \text{base–}H^+ \quad (2)$$

reagent purity,[9] many reactions were undertaken at 0 °C using the following sulfide-like reagents, bases,[10] and solvents: (a) Me_2S, tetramethylene sulfide, PhSMe, PhSH, tetramethylene selenide, Et_3P, $(Me_2N)_3P$, and $Ph_2PCH_2CH_2PPh_2$; (b) py, 2,2′-bipyridyl, 2,6-lutidine, 2,6-di-*tert*-butyl-4-methylpyridine (DBMP), α-picoline, γ-picoline, 3-bromopyridine, ethyl pyridine-2-carboxylate, pyrazine, 1-methylimidazole, 4-(dimethylamino)pyridine (DMAP), *N,N,N′,N′*-tetramethylethylenediamine (TMEDA), and ethyldiisopropylamine; (c) CH_3CN, CH_2Cl_2, CH_3NO_2, DMF, DMSO, and py.

The best results regarding the conversion of **1** to *N*-cyclohexyl-2,2-dimethyl-*N*-nitrosopropanamide (**1a**) were obtained by using (a) either Me_2S, tetramethylene sulfide, or PhSMe; (b) either pyridine, 2,2′-bipyridyl, or 2,6-lutidine as the base; and (c) acetonitrile as the solvent. For example, with 2 equiv of NO_2BF_4/Me_2S/py in CH_3CN, a 35% yield of **1a** (see Table I) was reached; an excess of reagent increased the yield of **1a** up to 50–55%. Surprisingly, the use of tetramethylene selenide and the different P(III) derivatives instead of a sulfide gave no **1a** at all, independently of the other factors. Even more striking is the fact that, not taking into account 2,6-lutidine and 2,2′-bipyridyl, *pyridine afforded much higher yields of* **1a** *than either stronger or weaker bases, but when pyridine was used as solvent the yield of* **1a** *was 0%, as if no base had been added*! No **1a** was obtained with the above-

(1) For related general reviews, see: (a) Challis, J. A. In *The Chemistry of Amides*; Zabicky, J., Ed.; Wiley-Interscience: London, 1970. (b) Regitz, M. In *The Chemistry of Diazonium and Diazo Groups*; Patai, S., Ed.; Wiley: Chichester, 1978. (c) Challis, B. C.; Challis, J. A. In *Comprehensive Organic Chemistry*; Barton, D. H. R., Ollis, W. D., Eds.; Pergamon Press: Oxford, 1979; Vol. 2.

(2) (a) Garcia, J.; González, J.; Segura, R.; Urpí, F.; Vilarrasa, J. *J. Org. Chem.* **1984**, *49*, 3322 and references therein. (b) Garcia, J. Doctoral Thesis, Universitat de Barcelona, 1986. (c) Berenguer, R.; Garcia, J.; Vilarrasa, J. *Synthesis*, in press.

(3) (a) Garcia, J.; González, J.; Segura, R.; Vilarrasa, J. *Tetrahedron* **1984**, *16*, 3121. (b) For related papers on nitrosopeptides, see: Challis, B. C.; Milligan, J. R.; Mitchell, R. C. *J. Chem. Soc., Chem. Commun.* **1984**, 1050 and references therein.

(4) (a) White, E. H. *J. Am. Chem. Soc.* **1955**, *77*, 6008 and references therein; (b) 6011; (c) 6014.

(5) France, H.; Heilbron, I. M.; Hey, D. H. *J. Chem. Soc.* **1940**, 369.

(6) (a) Garcia, J.; Vilarrasa, J. *Tetrahedron Lett.* **1982**, *23*, 1127; (b) **1987**, *28*, 341.

(7) Preliminary experiments with N_2O_4/py in CH_2Cl_2 were performed by J. Garcia some years ago.[2b] These conditions have also been employed in another context: Larm, O. *Carbohydr. Res.* **1975**, *43*, 192. Forrest, A. K.; Schmidt, R. R. *Tetrahedron Lett.* **1984**, *25*, 1769.

(8) Olah, G. A.; Gupta, B. G. B.; Narang, S. C. *J. Am. Chem. Soc.* **1979**, *101*, 5317.

(9) It has been just shown that some commercial samples of NO_2BF_4 contain significant percentages of $NOBF_4$ (Elsenbaumer, R. L. *J. Org. Chem.* **1988**, *53*, 437). The purity of the reagent used by us, ca. 97% according to Fluka, was alternatively checked (i) by its reaction with *p*-nitrotoluene (96% of dinitrotoluene was obtained after 1 h) and (ii) indirectly, by determination of the nitrosonium content, taking advantage of the fact that amides are N-nitrosated much faster than N-nitrated[2] (treatment of a simple amide, PhCONHMe, with 1 equiv of NO_2BF_4 and 1.5 equiv of pyridine in CH_3CN for 30 min at 0 °C gave only a 7% yield of *N*-nitroso derivative). Thus, we have assumed along this work that the reagent purity was 95 ± 2%.

(10) Complexation of NO_2^+ and NO^+ ions by pyridines is well-known: Olah, G. A.; Olah, J. A.; Overchuk, N. A. *J. Org. Chem.* **1965**, *30*, 3373. Cupas, C. A.; Pearson, R. L. *J. Am. Chem. Soc.* **1968**, *90*, 4742. Olah, G. A.; Narang, S. C.; Pearson, R. L.; Cupas, C. A. *Synthesis* **1978**, 452. Olah, G. A.; Narang, S. C.; Olah, J. A.; Pearson, R. L.; Cupas, C. A. *J. Am. Chem. Soc.* **1980**, *102*, 3507. In eq 2, the base and the sulfide (or related reagent) will probably compete for the nitronium ion.

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Table I. Percent Yield of Nitrosation[a] of 1–5

reagent	reactn time, h	1	2	3	4	5
$NO_2BF_4/Me_2S/py$[b]	2	35	75	65	75[e]	40[e]
	12	35	75			
$NO_2BF_4/Me_2S/py$[c]	2	50	100	100	100[e]	100[e]
	12	55				
$NOBF_4/py$[d]	2	62	100	100	100[e]	100[e]
	12	100				

[a] At 0 °C, from 1 mmol of **1–5** in 5 mL of CH_3CN. [b] Two millimoles of NO_2BF_4, 2 mmol of Me_2S, and 2 mmol of py per CONH group. [c] Four to five millimoles of $NO_2BF_4/Me_2S/py$ for **1–3**, 6–7 mmol for **4** and **5**. [d] Two millimoles of $NOBF_4$ and 2 mmol of py per CONH group. [e] These values are the yields of the dinitrosated product; the carbamate function was readily nitrosated in all cases.

Table II. Percent Yield of Nitrosation[a] of 1 with $NOBF_4$ after 2 h

base	solvent	yield	base	solvent	yield
py	CH_3CN	62	py	CH_2Cl_2[c]	25
2,2′-bipyridyl	CH_3CN	61	α-picoline	CH_3CN	24
2,6-lutidine	CH_3CN	52	py	DMSO	19
DBMP	CH_3CN	37	pyrazine	CH_3CN	5
3-bromopyridine	CH_3CN	35	1-methylimidazole	CH_3CN	0
py	DMF	33	γ-picoline	CH_3CN	0
2,2′-bipyridyl[b]	CH_3CN	30	DMAP	CH_3CN	0
py	CH_3NO_2	30	py	py	0

[a] From 1 mmol of **1**, 2 mmol of $NOBF_4$, and 2 mmol of base in 5 mL of solvent at 0 °C. [b] Only 1 mmol of bipyridyl. [c] When 2 mmol of 18-crown-6 was added, the yield increased up to 46%; in the presence of 18-crown-6 but without py, the yield was 0%.

mentioned solvents (other than CH_3CN), although in the case of CH_2Cl_2 and CH_3NO_2, the slight solubility of NO_2BF_4 may be partially responsible for such poor results.

Similar results were obtained with **2** and **3**. Thus, in the nitrosation of **2**, the best yields were also obtained by using sulfides and pyridine or 2,6-lutidine in acetonitrile (75% of methyl *N*-acetyl-*N*-nitroso-L-valinate (**2a**) with 2 equiv of $NO_2BF_4/Me_2S/py$, and 100% of **2a** with an excess of reagent; see Table I). With all remaining bases, yields of **2a** were lower.[11] Moreover, an excess of any base—more than 6–10 equiv, depending on the case—showed no beneficial effect; rather, the yields decreased. Similar yields of methyl *N*-acetyl-*N*-nitroso-L-isoleucinate (**3a**) were obtained from **3**.[12]

In order to gain insight into whether the S–ONO species or the solvated/coordinated nitrosonium ion was the nitrosating agent actually involved under our conditions, we investigated the direct nitrosation of **1**, **2**, and **3** with $NOBF_4$ in the presence of a base (eq 3).

$$RCONHR + NO^+ + base \rightarrow RCON(NO)R + base\text{–}H^+ \quad (3)$$

Despite a report[13] indicating that treatment of simple anions $CH_3CON^-CH_2R$, prepared from amides and sodium hydride, with $NOBF_4$ gave the corresponding nitrosoamides in low yields, we undertook a series of nitrosation reactions using several bases (see b, above) in different solvents (see c, above). For **1**, the results are collected in Table II, from which it is deduced that *again the combination of pyridine or 2,2′-bipyridyl as the base and CH_3CN as the solvent afforded the highest conversion yields; thus, pyridine turned out to be superior to either stronger* (1-methylimidazole, DMAP,...) *or weaker* (3-bromopyridine, pyrazine) *bases*.[14] Similar relative results were obtained in the case of **2**.[15]

In comparing the first and third rows of Table I, it is clearly seen that NO^+ is better than the NO_2^+/Me_2S mixture, indicating that the solvated NO^+ species is more active than the S–ONO species or that the nitrosating power of the NO_2^+/Me_2S mixture may only rely on the true NO^+ concentration in the medium (eq 1)[8] under our conditions.

In summary, it appears that polynitrosation of peptides may be quantitatively performed in cold CH_3CN by using either $NO_2BF_4/R_2S/py$ or $NOBF_4/py$,[16] in the ratios and addition order indicated in the Experimental Section, but only partially by using other nitrosating agents, solvents, bases,[14] etc. For the quantitative nitrosation of the more hindered amide bonds (e.g., **1**), the latter reagent mixture is recommended.

Experimental Section

^1H and ^{13}C NMR spectra were obtained in $CDCl_3$ on a Varian XL-200 spectrometer; chemical shifts are given in parts per million with respect to internal Me_4Si, and *J* values are in hertz. IR spectra were recorded in CCl_4 on a Perkin-Elmer 681 instrument; only the most significant absorptions (in cm^{-1}) are indicated. Elemental analyses were performed with a Perkin-Elmer 240 analyzer (Centro de Investigación y Desarrollo, CSIC, Barcelona). NO_2BF_4 (Fluka) and $NOBF_4$ (Merck) were employed as purchased. Tetramethylene sulfide and tetramethylene selenide were prepared according to ref 17. Compounds **1–6** are known.[18] We

(11) With 2 equiv of NO_2BF_4/Me_2S in CH_3CN, the yields of **2a** after 2 h were as follows: α-picoline, 50%; 1-methylimidazole and DBMP, 25%; γ-picoline, 20%; 3-bromopyridine, ethyl pyridine-2-carboxylate, and DMAP, ca. 10%; the others, 0%.

(12) It should be noted that only nitrosoamides were detected in all cases. N-Nitrations were not observed, in contrast to what happens in the reaction of $PhNMe_2$ with NO_2^+/R_2S, NO_2^+/R_2Se, and NO_2^+/R_3P.[8]

(13) Simpson, J. M.; Kapp, D. C.; Chapman, T. M. *Synthesis* **1979**, 100.

(14) An explanation of the striking fact that pyridine is the optimum one may be as follows: the more basic pyridines strongly coordinate the nitrosonium and nitronium ions to the extent that the electrophilicity of these cations is diminished, whereas the weaker bases cannot completely neutralize the acid produced in the reaction, so that eq 3 is not shifted enough to the right. In fact, nitrosation does not occur without a base, but an excess of base is detrimental, since coordination and/or solvation of the nitrosating agents may then decrease the rate of transfer to the amide group. Sterically hindered bases such as DBMP, in forming presumably weaker complexes with the nitrosating agents, should be beneficial in the first connection, but the proton may be transferred too slowly in the subsequent step(s).

(15) Yields of **2a** within 30 min: 100% with py and 2,6-lutidine, 85% with DBMP and 3-bromopyridine, 67% with α-picoline, 20% with 1-methylimidazole, and 15% with γ-picoline.

(16) *N*-Formyl-L-methionyl-L-leucyl-L-phenylalanine benzyl ester (OHC-Met-Leu-Phe-OCH_2Ph, **6**) can be quantitatively tri-N-nitrosated within 2 h with 6 equiv of $NOBF_4/py$.

(17) Brandsma, L.; Wijers, H. E. *Recl. Trav. Chim. Pays-Bas* **1963**, *82*, 68.

prepared **1-3** by simple acylation of cyclohexylamine, methyl L-valinate, and methyl L-isoleucinate, respectively, while Z-Ile-Val (the precursor of **4**) and **5** were purchased from Sigma.

Nitrosation of 1-5 with NO_2BF_4. Typical Procedure. To a stirred, ice-cooled solution of 183 mg (1.0 mmol) of **1**, 124 mg (2.0 mmol) of Me_2S, and ca. 160 mg (2.0 mmol) of anhydrous pyridine in 5 mL of anhydrous CH_3CN was added 264 mg (2.0 mmol) of NO_2BF_4, under N_2. After 2 h, the solution was added to CH_2Cl_2 and cold H_2O. The organic layer was isolated, washed again, and dried. Elimination of the solvent in vacuo, without heating, and separation of the residue by filtration through a short column of silica gel, with cold CH_2Cl_2 as eluent, afforded 75 mg (35%) of **1a**; then, 110 mg (60%) of **1** was recovered. (See Table I for experiments carried out at different reaction times or with an excess of reagent.)

N-Nitroso derivatives **2a** and **3a** were similarly prepared. For the nitrosation of **4** and **5**, double amounts of Me_2S, pyridine, and NO_2BF_4 were used (see Table I).

1a: yellow oil; dec[19] at 40-42 °C; ^1H NMR δ 1.15 (s, 9 H), 1.0-2.0 (m, 10 H), 4.40 (m, 1 H); IR 1715, 1510. It affords, in refluxing CH_2Cl_2, cyclohexyl pivalate [bp 97-99 °C at 16 Torr (lit.[20] bp 87 °C at 12 Torr)] in 78% yield.

2a: yellow oil; bp 40 °C (furnace temperature) at 0.10 Torr; ^1H NMR δ 0.55 (d, J = 6.8, 3 H), 1.10 (d, J = 6.6, 3 H), 2.40 (m, 1 H), 2.81 (s, 3 H), 3.62 (s, 3 H), 4.89 (d, J = 9.0, 1 H); IR 1755, 1740. Anal. Calcd for $C_8H_{14}N_2O_4$: C, 47.52; H, 6.98; N, 13.85. Found: C, 47.36; H, 7.20; N, 13.52. Treatment of **2a** with pyrrolidine[3a] in CH_2Cl_2 affords readily methyl 2-diazo-3-methylbutanoate (identical by TLC, ^1H NMR, and IR with an authentic sample[3a,21]).

3a: yellow oil; bp 45 °C (furnace temperature) at 0.10 Torr; ^1H NMR 0.70 (m, 1 H), 0.76 (m, 3 H), 0.98 (m, 2 H), 1.07 (d, J = 6.6, 3 H), 2.20 (m, 1 H), 2.81 (s, 3 H), 3.61 (s, 3 H), 4.95 (d, J = 9.2, 1 H); IR 1760, 1740. Anal. Calcd for $C_9H_{16}N_2O_4$: C, 49.99; H, 7.46; N, 12.96. Found: C, 49.50; H, 7.70; N, 12.95. Treatment of **3a** with pyrrolidine[3a] in CH_2Cl_2 affords readily methyl 2-diazo-3-methylpentanoate [yellow oil; R_f = 0.45 (Merck aluminum sheets of silica gel 60 F_{254}; CH_2Cl_2); ^1H NMR δ 0.96 (t, J = 6.8, 3 H), 1.15 (d, J = 6.8, 3 H), 1.45 (m, 2 H), 2.4 (m, 1 H), 3.77 (s, 3 H); IR 2090, 1690].[21]

***N*-Benzyloxycarbonyl-*N*-nitroso-L-isoleucyl-*N*-nitroso-L-valine methyl ester (4a)**: yellow oil (nondistillable);[19] ^1H NMR δ 0.40 (d, J = 7.0, 3 H), 0.83 (m, 4 H), 1.05 (d, J = 6.6, 6 H), 1.10 (m, 1 H), 2.44 (m, 1 H), 2.55 (m, 1 H), 3.57 (s, 3 H), 4.81 (d, J = 8.8, 1 H), 5.48 (s, 2 H), 5.79 (d, J = 9.6, 1 H), 7.40 (m, 5 H); ^{13}C NMR δ 11.1 (CH_3CH_2), 17.0 (CH_3CHCH_2), 18.7 (CH_3CHCH_3), 21.5 (CH_3CHCH_3), 24.3 (CH_2CH_3), 27.2 (CH), 33.0 (CH), 52.3 (CH_3O), 57.7 (CHCO), 58.2 (CHCO), 70.2 (CH_2O), 128.4 (CH), 128.8 (CH), 128.9 (CH), 134.3 (C), 153.3 (OCON), 167.2 (CON), 169.7 (COO); IR 1760, 1730 (br).

***N*-Benzyloxycarbonyl-*N*-nitroso-L-valyl-*N*-nitroso-L-leucine methyl ester (5a)**: yellow oil (nondistillable);[19] ^1H NMR δ 0.73 (d, J = 7.0, 3 H), 0.80 (d, J = 7.0, 3 H), 0.84 (d, J = 7.0, 3 H), 1.15 (m, 1 H), 1.10 (d, J = 6.6, 3 H), 1.42 (ddd, J = 14.4, 8.9, 5.6, 1H), 1.88 (ddd, J = 14.4, 8.8, 5.2, 1 H), 2.81 (d of heptuplets, J = 9.2, 6.8, 1 H), 5.17 (dd, J = 8.8, 5.6, 1 H), 5.48 (s, 2 H), 5.66 (d, J = 9.2, 1 H), 7.40 (m, 5 H); ^{13}C NMR δ 18.1 (CH_3CH), 20.8 (CH_3CH), 21.7 (CH_3CH), 22.7 (CH_3CH), 25.0 (CH_3CHCH_3), 27.0 (CH_3CHCH_3), 36.7 ($CHCH_2CH$), 51.4 (CHCO), 52.6 (CH_3O), 58.9 (CHCO), 70.2 (CH_2O), 128.2 (CH), 128.8 (CH), 128.9 (CH), 134.2 (C), 153.4 (OCON), 167.8 (CON), 169.5 (COO); IR 1760-1740.

Nitrosation of 1-5 with $NOBF_4$. Typical Procedure. To a stirred solution of 183 mg (1.0 mmol) of **1** and 160 mg (2 mmol) of anhydrous pyridine in 5 mL of CH_3CN, cooled at -20 °C, was added 232 mg (2.0 mmol) of $NOBF_4$. The solution was maintained at 0 °C under N_2 for 2 h and then added to CH_2Cl_2 and ice. The organic layer was further extracted with cold H_2O and dried and the solvent eliminated in vacuo without heating, to yield a yellow residue containing only **1a** and **1** (TLC and ^1H NMR), which were separated by filtration through a small column of silica gel with cold CH_2Cl_2 as eluent, to afford 131 mg (62%) of chromatographically and spectroscopically pure **1a**.

Compounds **2a**, **3a**, **4a**, and **5a**, were similarly prepared, although 4 mmol of $NOBF_4$ and pyridine were employed in the case of **4a** and **5a**. Other related experiments, performed in the same way but with a change in the base or the solvent, are summarized in Table II.

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(18) (a) Tisue, G. T.; Linke, S.; Lwowski, W. *J. Am. Chem. Soc.* **1967**, *89*, 6303. (b) Reihlen, H.; Knöpfle, *Justus Liebigs Ann. Chem.* **1936**, *523*, 199. (c) Applewhite, T. H.; Waite, H.; Niemann, C. *J. Am. Chem. Soc.* **1958**, *80*, 1465. (d) Lloyd, K.; Young, G. T. *J. Chem. Soc. C* **1971**, 2890. (e) Okada, Y.; Iguchi, S.; Hirai, T.; Goto, Y.; Yagyu, M.; Yajima, H. *Chem. Pharm. Bull.* **1984**, *32*, 4608 and ref 3a. (f) Martinez, J.; Laur, J.; Castro, B. *Tetrahedron* **1985**, *41*, 739.

(19) These nitroso derivatives are oils that are very sensitive to heat, which precludes purification by distillation (even at 0.10-0.01 Torr), so that elemental analysis cannot be used as the standard of purity. Attempts to determine their exact molecular mass were unsuccessful due to the extensive decomposition of the samples at the temperature required (40-50 °C) to detect any signal. Thus, we had to rely upon the lack of other spots on TLC—nitroso derivatives afford intense yellow spots, whereas unnitrosated CONH groups are clearly revealed by the chlorine-tolidine method (see: Reindel, F.; Hoppe, W. *Chem. Ber.* **1954**, *87*, 1103)—and the absence of unexpected peaks in the ^1H NMR spectra (200 MHz, below 18 °C) as purity criteria.

(20) Tinkelenberg, A.; Kooyman, E. C.; Louw, R. *Recl. Trav. Chim. Pays-Bas* **1972**, *91*, 3.

(21) Also see: Takamura, N.; Mizoguchi, T.; Koga, K.; Yamada, S. *Tetrahedron* **1975**, *31*, 227.

Convenient Synthesis of 4-Methylhistamine and Racemic α,4-Dimethylhistamine and α,4-Dimethylhistidine

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The search for selective histamine agonists and antagonists remains one of the most active fields in medicinal chemistry. An important compound in this area, 4-methylhistamine (**1**), a selective H_2 agonist, is valuable as both a pharmacological standard and chemical intermediate. Recently, α,4-dimethylhistamine (**2**) has been found to be more selective than **1** as an H_2 agonist, with the *S* isomer having the greater specificity.[1,2] In support of a program in this area, it became necessary to prepare both **1** and **2**, as well as the unreported histidine analogue **3**. The reported preparations for **1**[3,4] and **2**[2,5,6] require tedious isolation procedures, provide low overall yields, and are inconvenient for large-scale synthesis. We now report a convenient method for the synthesis of compounds **1-3** which provides good overall yields and is well suited toward large-scale preparation.

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