Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

A Convenient Method for the Preparation of N-Aryl and N-Alkyl-O-Methyl Hydroxylamines

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Published online: 23 Sep 2006.

To cite this article: Paulo F. Santos , Ana M. Lobo & Sundaresan Prabhakar (1995) A Convenient Method for the Preparation of N-Aryl and N-Alkyl-O-Methyl Hydroxylamines, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 25:22, 3509-3518, DOI: 10.1080/00397919508015485

To link to this article: http://dx.doi.org/10.1080/00397919508015485

SYNTHETIC COMMUNICATIONS, 25(22), 3509-3518 (1995)

A CONVENIENT METHOD FOR THE PREPARATION OF *N*-ARYL AND *N*-ALKYL-*O*-METHYL HYDROXYLAMINES.

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ABSTRACT: Trifluoroaceto or *p*-nitrobenzo-*N*-substituted hydroxamic acids are smoothly methylated with diazomethane and the products cleanly cleaved by hydrazine to provide the title compounds.

In connection with our studies on the substitution reactions of trivalent nitrogen compounds bearing a methoxy group as a nucleofuge, a variety of *N*-aryl and *N*-alkyl-*O*-methyl hydroxylamines were required. A preparatively useful method involving *O*-alkylation of *N*-alkyl or *N*-aryl-*N*-hydroxyureas followed by aminolysis of these derivatives with an organic base such as diethylamine or *p*-anisidine to liberate the *O*-alkyl hydroxylamines has been reported.[1-3] An alternative mild procedure employing trifluoroacetohydroxamic acid as a suitable

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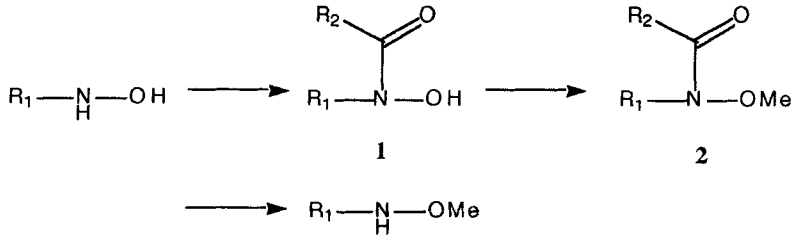
precursor for *N*-phenyl-*O*-methyl hydroxylamine had been briefly mentioned.[4] We describe here an extension and a modification of this convenient method for the synthesis of various *N*-aryl or *N*-alkyl-*O*-methyl hydroxylamines (**Scheme**). The requisite starting materials, the 4-nitrobenzo-*N*-aryl or *N*-alkyl hydroxamic acids,[5] were obtained in excellent yield by acylation of the respective hydroxylamines with the acid chloride in ether in the presence of aqueous sodium bicarbonate.[6] An ethereal solution of the above acids, on exposure to the action of diazomethane[7] afforded the corresponding methyl ethers in excellent yields. The *N*-methoxyanilines, liberated efficiently from these compounds in tetrahydrofuran by hydrazinolysis at room temperature, required, in general, special work-up procedure since they form azobenzenes in varying porportions, in concentrated solutions, in the solid phase or on attempted purification by distillation.[2,3]

The preferred method to remove the hydrazide formed and the excess hydrazine used in the reaction was to add an equal volume of *n*-hexane to the tetrahydrofuran solution, concentrating the solution to its original volume and repeating the process until copious precipitation of the hydrazide was observed. Filtration of the chilled mixture provided an hexane solution of virtually pure *N*-methoxyanilines[9] which was used directly, after drying, for our studies. The *N*-alkyl-*O*-methyl hydroxylamines, however, were difficult to obtain by hydrazinolysis at room temperature from the corresponding 4-nitrobenzohydroxamic acid derivatives. This lack of reactivity probably reflects the reduced electrophilicity of the carbonyl group and diminished leaving group ability of the *N*-alkyl-*N*-methoxy amines *vis*-à-*vis* their aromatic counterparts. Nevertheless these compounds were obtained without difficulty, and in good yields, by cleavage of the corresponding trifluoroaceto--hydroxamic acid *O*-methyl ethers with hydrazine at room temperature.

In conclusion, an efficient and a convenient procedure for the preparation of



SCHEME

methoxyamines is described. *N*-substitution reactions of these substrates with various nucleophiles with be reported elsewhere.

Experimental

Melting points were determined with a hot-stage microscope Reichert Thermovar and are uncorrected. Chromatography was performed using E. Merck silica gel 60 (70-230 mesh). Infrared spectra (IR) were recorded with a Perkin-Elmer 157 Gand 683 grating infrared spectrophotometer and frequencies reported in cm^{-1}. Proton nuclear magnetic resonance spectra (^1H NMR) were obtained at 300 MHz with a Varian Unit 300 spectrometer. Chemical shifts are reported in ppm downfield from tetramethylsilane. High resolution spectra (HREIMS) was measured in a Kratos MS-25 RF instrument using electron impact at 70 eV. Elemental analyses were carried out at the micro-analytical division of DTIQ-INETI, Queluz, Portugal.

General Procedure for the Preparation of 4-Nitrobenzo-*N*-Aryl or *N*-Alkyl Hydroxamic Acids (1).

A vigorously stirred mixture of the hydroxylamine (7.7 mmoles), sodium bicarbonate (1.2 eq) in an ether-water mixture (10:1 ; v/v) (55 ml) at 0°C was treated

dropwise with a solution of 4-nitrobenzoyl chloride (1 eq) in dry ether (20 ml). After the addition was complete the reaction mixture was allowed to attain room temperature and stirring continued until the reaction was complete (tlc control). More ether was added to dissolve any precipitated hydroxamic acid, the ethereal solution was washed with water (2 x 20 ml) and dried (Na_2SO_4). Evaporation of the solvent yielded the product which was crystallised from a suitable solvent (see **Tables 1** and **2**).

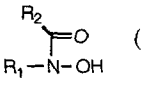
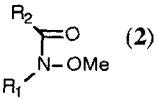
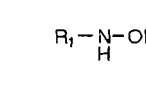
General Procedure[4] for the Preparation of Trifluoroaceto-*N*-Aryl or *N*-Alkyl Hydroxamic Acids (2).

The *N*-substituted hydroxylamine (9.8 mmoles) in dry ether (25 ml), cooled to -80°C, was treated dropwise with an ethereal solution (20 ml) of trifluoroacetic anhydride (1.2 eq) with stirring during 30 minutes. When the reaction was adjudged to be complete (tlc control), the mixture was washed with cold aqueous bicarbonate solution (3%) (15 ml) and then with water (2 x 20 ml) and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure yielded the hydroxamic acids **1g** and **1k** as solids. The hydroxamic acids **1i**, **1l** and **1m** were isolated by rapid extraction from the ether solution with ice-cold aqueous sodium hydroxide solution (5%) followed by immediate acidification to pH 4 with cold aqueous hydrochloric acid (5%). The liberated acids were extracted with CH_2Cl_2, washed with water, dried (Na_2SO_4) and the solvent evaporated to afford the hydroxamic acids as solids which were crystallised from a suitable solvent (see **Tables 1** and **2**).

General Procedure for the Methylation of Hydroxamic Acids.

The hydroxamic acid (3.8 mmoles) was added in portions to an excess of diazomethane (5 eq) in ether (60 ml) at 0°~5°C. Evaporation of the solvent after completion of the reaction (tlc control) under reduced pressure yielded the *O*-methyl ethers, which were purified by column chromatography and crystallised from a suitable solvent (see **Tables 1** and **3**).

Table 1

Substance	 (1)			 (2)		 (3)		
	Yield (%)	m.p.°C (solvent[a]) obs.	lit ref.	Yield (%)	m.p.°C (solvent[a]) obs.	Yield (%)	m.p.°C (solvent[a]) obs.	lit ref.
a) R_1=Ph; R_2=4-$NO_2C_6H_4$	98	164-165 (A)	163[10]	77	73-74 (D)	87	oil	oil[2]
b) R_1=3-MeC_6H_4; R_2=4-$NO_2C_6H_4$	92	171-172 (A)	158[11]	73	86-87 (D)	72	oil	—
c) R_1=4-MeC_6H_4; R_2=4-$NO_2C_6H_4$	88	143-144 (A)	143[12]	68	108-109 (D)	98	oil	—
d) R_1=2-ClC_6H_4; R_2=4-$NO_2C_6H_4$	98	146-148 (B)		83	89-90 (E)	87	oil	—
e) R_1=4-ClC_6H_4; R_2=4-$NO_2C_6H_4$	83	120-121 (B)	123[13]	85	129-130 (E)	90	oil	—
f) R_1=4-$CO_2MeC_6H_4$; R_2=4-$NO_2C_6H_4$	88	183(dec.) (B)		79	125-126 (E)	90	57-58 (E)	—
g) R_1=CH_2Ph; R_2=4-$NO_2C_6H_4$	88	138-140 (B)		85	58-59 (D)			
h) R_1= cyclohexyl; R_2=4-$NO_2C_6H_4$	64	170-171 (B)	164[2]	63	58-60 (E)			
i) R_1=CH_2Ph; R_2=CF_3	90	70-71 (C)		95	oil	87	145[b] (F) (HCl salt)	163[2] (HCl salt)
j) R_1= cyclohexyl; R_2=CF_3	95	82-83 (C)		87	oil	75	144 (G) (HCl salt)	143-145[14] (HCl salt)
k) R_1=4-$CO_2MeC_6H_4$; R_2=CF_3	81	141 (dec.) (C)						
l) R_1=4-MeC_6H_4; R_2=CF_3	91	80-81 (C)						
m) R_1=4-ClC_6H_4; R_2=CF_3	78	106-107 (C)						

a) Solvent: A = C_6H_6/pet. ether; B = CH_2Cl_2/pet. ether; C = *n*-hexane; D = CH_2Cl_2/*n*-hexane; E = Et_2O/pet. ether; F = EtOAc; G = MeOH/Et_2O.
b) Found: C 55.73; H 7.11; N 8.05. Calculated for $C_8H_{12}ClNO$: C 55.34; H 6.97; N 8.07%.

Table 2

Substance	IR cm^{-1} (KBr)	^1H NMR Chemical Shift (δ) ppm	Molecular Formula	Elemental Analysis (%) Found (Calculated) C	H	N	Accurate M^+ Found (Calculated)
1b	3110, 1640	9.02 (1H, bs, exch D_2O, O*H*) 2.32 (3H, s, C*Me*) ($CDCl_3$)	$C_{14}H_{12}N_2O_4$	—	—	—	272.0798 (272.0879)
1d	3130, 1655	8.78 (1H, bs, exch D_2O, O*H*) ($CDCl_3$)	$C_{13}H_9ClN_2O_4$	53.34 (53.35)	3.04 (3.10)	9.47 (9.57)	—
1f	3280, 1690, 1660	11.19 (1H, bs, exch D_2O, *OH*) 3.86 (3H, s, O*Me*) (DMSO-d_6)	$C_{15}H_{12}N_2O_6$	57.02 (56.97)	4.03 (3.82)	8.69 (8.86)	—
1g	3110, 1605	10.31 (1H, bs, exch D_2O, O*H*) 4.88 (2H, s, CH_2Ph) (DMSO-d_6)	$C_{14}H_{12}N_2O_4$	61.91 (61.76)	4.43 (4.44)	10.11 (10.29)	—
1h	3170, 1610	9.79 (1H, m exch D_2O, O*H*) 4.25 (1H, bs, N-C-*H*) (DMSO-d_6)	$C_{13}H_{16}N_2O_4$	59.16 (59.08)	6.23 (6.10)	10.69 (10.60)	—
1i	3260, 1675	9.90 (1H, bs, exch D_2O, O*H*) 4.86 (2H, s, CH_2Ph) (acetone-d_6)	$C_9H_8F_3NO_2$	49.35 (49.32)	3.85 (3.68)	6.27 (6.39)	—
1g	3230, 1660	9.36 (1H, bs, exch D_2O, O*H*) 4.21-4.11 (1H, m, N-C-*H*) (acetone-d_6)	$C_8H_{12}F_3NO_2$	45.51 (45.50)	5.76 (5.73)	6.46 (6.63)	—
1k	3260, 1710, 1695	10.78 (1H, bs, exch D2O, O*H*) 3.89 (3H, s, O*Me*) (acetone-d_6)	$C_{10}H_8F_3NO_4$	45.56 (45.64)	3.03 (3.06)	5.15 (5.32)	—
1l	3260, 1665	10.47 (1H, bs, exch D_2O, O*H*) 2.34 (3H, s, C*Me*) (acetone-d_6)	$C_9H_8F_3NO_2$	49.47 (49.32)	3.92 (3.68)	6.38 (6.39)	—
1m	3210, 1675	10.65 (1H, bs, exch D_2O, O*H*) (acetone-d_6)	$C_8H_5ClF_3NO_2$	39.93 (40.11)	2.31 (2.10)	5.68 (5.85)	—

Table 3

Substance	IR cm^{-1} (KBr)	^1H NMR Chemical Shift (δ) ppm ($CDCl_3$)	Molecular Formula	Elemental Analysis (%) Found (Calculated) C	H	N	Accurate $[M + NH_4]^+$ Found (Calculated)
2a	1670	3.67 (3H, s, O*Me*)	$C_{14}H_{12}N_2O_4$	62.01 (61.76)	4.62 (4.44)	10.31 (10.29)	—
2b	1645	3.67 (3H, s, O*Me*) 2.38 (3H, s, C*Me*)	$C_{15}H_{14}N_2O_4$	62.76 (62.93)	5.19 (4.93)	9.96 (9.78)	—
2c	1640	3.68 (3H, s, O*Me*) 2.37 (3H, s, C*Me*)	$C_{15}H_{14}N_2O_4$	63.09 (62.93)	5.13 (4.93)	9.58 (9.78)	—
2d	1675	3.80 (3H, bs, O*Me*)	$C_{14}H_{11}ClN_2O_4$	54.89 (54.83)	3.73 (3.61)	9.01 (9.13)	—
2e	1650	3.63 (3H, s, O*Me*)	$C_{14}H_{11}ClN_2O_4$	55.12 (54.83)	3.90 (3.61)	9.25 (9.13)	—
2f	1710, 1660	3.87[a] (3H, s, CO_2*Me*) 3.62[a] (3H, s, O*Me*)	$C_{16}H_{14}N_2O_6$	58.39 (58.18)	4.53 (4.27)	8.31 (8.48)	—
2g	1635	4.96 (2H, s, CH_2Ph) 3.45 (3H, s, O*Me*)	$C_{15}H_{14}N_2O_4$	63.01 (62.93)	5.15 (4.93)	9.77 (9.78)	—
2h	1640	4.20 (1H, m, N-C-*H*) 3.52 (3H, s, O*Me*)	$C_{14}H_{18}N_2O_4 + NH_4$[c]	—	—	—	296.1607 (296.1610)
2i	1700[b]	4.86 (2H, s, CH_2Ph) 3.73 (3H, s, O*Me*)	$C_{10}H_{10}F_3NO_2 + NH_4$[c]	—	—	—	251.1002 (251.1007)
2j	1700[b]	4.07 (1H, m, N-C-*H*) 3.84 (3H, s, O*Me*)	$C_9H_{14}F_3NO_2 + NH_4$[c]	—	—	—	243.1304 (243.1320)

a) In DMSO-d_6. b) Film. c) By chemical ionization.

Table 4

Substance	IR cm^{-1} (medium)	^1H NMR Chemical Shift (δ) ppm ($CDCl_3$)
3a	—	7.04 (1H, bs, exch D_2O, N*H*) 3.77 (3H, s, O*Me*)
3b	3290 (film)	6.98 (1H, bs, exch D_2O, N*H*) 3.76 (3H, s, O*Me*) 2.32 (3H, s, C*Me*)
3c	—	6.96 (1H, bs, exch D_2O, N*H*) 3.75 (3H, s, O*Me*) 2.29 (3H, s, C*Me*)
3d	3290 (film)	7.43 (1H, bs, exch D_2O, N*H*) 3.81 (3H, s, O*Me*)
3e	3270 (film)	7.00 (1H, bs, exch D_2O, N*H*) 3.75 (3H, s, O*Me*)
3f	3260, 1695 (KBr)	3.88 (3H, s, CO_2 *Me*) 3.79 (3H, s, O*Me*)
3g	3260 (film)	5.64 (1H, bs, exch D_2O, N*H*) 4.06 (2H, s, CH_2Ph) 3.51 (3H, s, O*Me*)
3h	3250 (film)	5.40 (1H, bs, exch D_2O, N*H*) 3.54 (3H, s, O*Me*) 2.87-2.80 (1H, m, N-C-*H*)

General Procedure for the Preparation of *N*-Aryl or *N*-Alkyl-*O*-Methyl Hydroxylamines (3).

The hydroxamic acid *O*-methyl ether (1.0 mmol) in tetrahydrofuran (25 ml) was treated with hydrazine hydrate (4 eq) and the mixture stirred at room temperature until the reaction was complete (tlc control). *n*-Hexane was added (25 ml) and the solution concentrated to half its bulk under a stream of nitrogen — the process being repeated until most of tetrahydrofuran was replaced by *n*-hexane and a copious precipitate of 4-nitrobenzhydrazide was observed. The chilled mixture was then filtered and the filtrate dried (Na_2SO_4) leaving a solution of practically pure *O*-methyl hydroxylamine (see **Tables 1** and **4**).

ACKNOWLEDGMENTS

We thank PEDIP (Lisbon) for partial financial support and for the award of a fellowship to one of us (P. F. S.). Our thanks are also due to Dr. S. Narayanaswami, Pfizer (U.K.) for the interest shown in this work.

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(Received in the UK 23 March 1995)