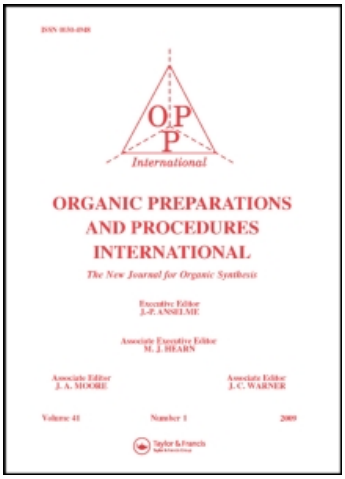

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PREPARATION OF RING-SUBSTITUTED PHENOXYAMINE DERIVATIVES

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PREPARATION OF RING-SUBSTITUTED PHENOXYAMINE DERIVATIVES

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(12/05/96)

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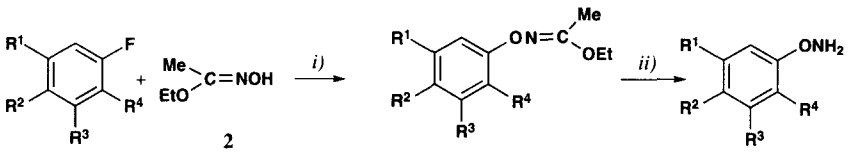
Phenoxyamine was first synthesized by O-amination of potassium phenoxide with hydroxylamine-*O*-sulfonic acid in low yield.[1] Recently some ring-substituted phenoxyamine derivatives have been used as herbicides and antibacterial agents,[2] and their synthesis have been carried out by a modification of the method of Bumgardner and Lilly.[3] Cadogan and Rowley reported facile synthesis of phenoxyamine by O-phenylation of *N*-hydroxyphthalimide with diphenyliodonium chloride followed by hydrazinolysis of *N*-phenoxyphthalimide.[4] Other phenoxyamine derivatives have been synthesized by amination of the corresponding sodium phenoxide derivatives in dimethylformamide (DMF) using 2,4-dinitrophenoxyamine.[5] Yields for this reaction are sensitive to the pK_a of the phenol and this method is suitable for the synthesis of oxygenated phenoxyamines having a tosyloxy or a mesyloxy group. For such amine acceptors, *O*-mesitylenesulfonylhydroxylamine[6] is a powerful aminating reagent; however, it is recommended that it be prepared immediately prior to use and that it not be stored to avoid explosions.[7]

On the other hand, nitrophenoxyamines have been synthesized by the reaction of nitrofluorobenzenes and ethyl acetohydroxamate (Zinner's method)[8,9] or *tert*-butyl *N*-hydroxycarbamate (Carpino's method)[9,10] with base followed by hydrolysis with acid. A number of substituted phenoxyamine derivatives have been synthesized by the application of these methods; however, the reaction is limited to the synthesis of phenoxyamine derivatives bearing strong *ortho* and/or *para* electron-withdrawing substituents such as 2- or 4-nitrophenoxy-, 2,4- or 2,6-dinitrophenoxy- and 2,4,6-trinitrophenoxy-amines.[9]

In the course of our investigation of the chemistry of *N*-aryloxyamides, we required some ring-substituted phenoxyamine derivatives. Since Zinner's method is convenient and safe, and ethyl acetohydroxamate is commercial availablely, we investigated its scope and limitations.



1 2 3 4

i) *t*-BuOK/DMF; *ii)* 70% $HClO_4$/dioxane

Substitution of fluorobenzenes by the potassium salt of ethyl acetohydroxamate in DMF was considerably influenced by the electronic nature of the substituents. The reaction was facilitated by electron-withdrawing groups in fluorobenzenes as expected. The fluorine atom was activated by a

combination of inductive and resonance effects of substituents in the benzene ring; in the case of halogen substituents which have these two effects in opposing directions, it was most activated by substituents at the *meta* position, probably due to a balancing of these effects (Table 1, entries 6, 7, 10 and 12). Hydrolysis of **3** with perchloric acid gave **4** in good yield.

TABLE 1. Synthesis of Phenoxyamines (**4**) from Fluorobenzenes (**1**)

Entry	**1**	R^1	R^2	R^3	R^4	**3**	**4**
1	**a**	H	H	NO_2	H	65.9	99.9
2	**b**	H	H	CN	H	66.8	78.3
3	**c**	H	CN	H	H	86.6	91.0
4	**d**	F	H	CN	H	80.3	92.3
5	**e**	H	F	H	F	55.4	97.2
6	**f**	F	H	F	H	62.1	64.0
7	**g**	Br	H	H	F	74.6	69.9
8	**h**	H	Cl	H	Cl	77.8	92.7
9	**i**	Br	H	H	Br	44.2	93.5
10	**j**	H	H	F	H	20.0	68.6
11	**k**	H	H	H	F	8.2	82.5
12	**l**	H	H	Cl	H	17.8	74.4
13	**m**	H	H	H	Cl	13.5	77.8
14	**n**	H	Cl	H	H	11.0	78.0

EXPERIMENTAL SECTION

Melting points are uncorrected and were taken on a Yanagimoto hot-stage melting point apparatus. ^1H NMR spectra were measured on a JEOL JNM-PMX60SI spectrometer with tetramethylsilane (Me_4Si) as an internal reference and $CDCl_3$ as the solvent. Infrared (IR) spectra were recorded on a JASCO IR810 spectrometer as KBr pellets. Low and high resolution mass spectra (MS) were obtained with a JEOL JMS-DX300 spectrometer with a direct inlet system at 70 eV. Elemental analyses were performed in the Microanalytical Laboratory of this University.

Typical Procedure. Synthesis of Ethyl 2,4-dichlorophenoxyacetohydroxamate (3i).- To **2** (2.56 g, 24.8 mmol) in DMF (25 mL) was added *t*-BuOK (3.06 g, 27.3 mmol) with ice cooling. After stirring the reaction mixture for 30 min at room temperature, 2,4-dichlorofluorobenzene (4.50 g, 27.3 mmol) was added and the reaction mixture was heated at 80° for 1.5 h. H_2O (150 mL) was added to the reaction mixture with ice cooling and the aqueous layer was extracted with ethyl acetate (100 mL x 2), and the combined organic layer was washed with brine (100 mL), dried over Na_2SO_4, and concentrated. The residue was chromatographed on a column of silica gel with benzene-hexane (2:1) as an eluent to give **3i** (4.79 g, 78%). The spectral data and elemental analyses are reported in Table 2 and 3.

TABLE 2. Spectral Data for New Compounds

Entry	Cmpd	^{1}H NMR (δ)	IR (cm^{-1})	EI-Mass *m/z* (%)
1	**3a**	1.37 (3H, t, *J* = 7.0, $C\underline{H}_3$-CH_2) 2.05 (3H, s, CH_3) 4.17 (2H, q, *J* = 7.0, CH_3-$C\underline{H}_2$) 7.17-8.03 (4H, m, Ar-H)	1645	224 (M^+, 99.5) 139 (100)
2	**3b**	1.33 (3H, t, *J* = 7.0, $C\underline{H}_3$-CH_2) 2.10 (3H, s, CH_3) 4.15 (2H, q, *J* = 7.0, CH_3-$C\underline{H}_2$) 6.93-7.53 (4H, m, Ar-H)	2220 1650	215 (M^+, 45.7) 119 (100)
3	**3c**	1.33 (3H, t, *J* = 7.0, $C\underline{H}_3$-CH_2) 2.10 (3H, s, CH_3) 4.16 (2H, q, *J* = 7.0, CH_3-$C\underline{H}_2$) 7.12 (2H, d, *J* = 9.0, Ar-H) 7.61 (2H, d, *J* = 9.0, Ar-H)	2230[a] 1650	204 (M^+, 54.8) 119 (100)
4	**3d**	1.36 (3H, t, *J* = 7.0, $C\underline{H}_3$-CH_2) 2.10 (3H, s, CH_3) 4.15 (2H, q, *J* = 7.0, CH_3-$C\underline{H}_2$) 6.63-7.27 (3H, m, Ar-H)	2250 1650	222(M^+, 46.4) 137(100)
5	**3e**	1.33 (3H, t, *J* = 7.0, $C\underline{H}_3$-CH_2) 2.11 (3H, s, CH_3) 4.12 (2H, q, *J* = 7.0, CH_3-$C\underline{H}_2$) 6.20-7.30 (3H, m, Ar-H)	1650[a]	215 (M^+, 37.0) 130 (100)
6	**3f**	1.33 (3H, t, *J* = 7.0, $C\underline{H}_3$-CH_2) 2.05 (3H, s, CH_3) 4.11 (2H, q, *J* = 7.0, CH_3-$C\underline{H}_2$) 6.00-6.85 (3H, m, Ar-H)	1620	215 (M^+, 71.0) 130 (100)
7	**3g**	1.33 (3H, t, *J* = 7.0, $C\underline{H}_3$-CH_2) 2.10 (3H, s, CH_3) 4.13 (2H, q, *J* = 7.0, CH_3-$C\underline{H}_2$) 6.53-7.67 (3H, m, Ar-H)	1650	275 (M^+, 40.2) 277 (M^++2, 39.2) 190 (100)
8	**3h**	1.33 (3H, t, *J* = 7.0, $C\underline{H}_3$-CH_2) 2.13 (3H, s, CH_3) 4.11 (2H, q, *J* = 7.0, CH_3-$C\underline{H}_2$) 6.83-7.23 (3H, m, Ar-H)	1650	247 (M^+, 56.3) 249 (M^++2, 36.1) 251 (M^++2, 6.2) 160 (100)
9	**3i**	1.33 (3H, t, *J* = 7.0, $C\underline{H}_3$-CH_2) 2.02 (3H, s, CH_3) 4.15 (2H, q, *J* = 7.0, CH_3-$C\underline{H}_2$) 6.82 (1H, dd, *J* = 8.5, 2.0, Ar-H) 7.23 (1H, d, *J* = 8.5, Ar-H) 7.43 (1H, d, *J* = 2.0, Ar-H)	1640	335 (M^+, 21.1) 337 (M^++2, 40.8) 339 (M^++2, 20.3) 267 (100)

a) Neat.

TABLE 2. continued

Entry	Cmpd	^{1}H NMR (δ)	IR (cm^{-1})	EI-Mass *m/z* (%)
10	**3j**	1.33 (3H, t, *J* = 7.0, C<u>H</u>$_3$-CH$_2$) 2.07 (3H, s, CH$_3$) 4.15 (2H, q, *J* = 7.0, CH$_3$-C<u>H</u>$_2$) 6.23-7.33 (4H, m, Ar-H)	1650[a]	197 (M$^+$, 35.2) 112 (100)
11	**3k**	1.33 (3H, t, *J* = 7.0, C<u>H</u>$_3$-CH$_2$) 2.12 (3H, s, CH$_3$) 4.15 (2H, q, *J* = 7.0, CH$_3$-C<u>H</u>$_2$) 6.70-7.55 (4H, m, Ar-H)	1650[a]	197 (M$^+$, 61.2) 112 (100)
12	**3l**	1.33 (3H, t, *J* = 7.0, C<u>H</u>$_3$-CH$_2$) 2.07 (3H, s, CH$_3$) 4.13 (2H, q, *J* = 7.0, CH$_3$-C<u>H</u>$_2$) 6.63-7.37 (4H, m, Ar-H)	1650[a]	213(M$^+$, 50.0) 215 (M$^+$+2, 16.9) 128 (100)
13	**3m**	1.33 (3H, t, *J* = 7.0, C<u>H</u>$_3$-CH$_2$) 2.17 (3H, s, CH$_3$) 4.16 (2H, q, *J* = 7.0, CH$_3$-C<u>H</u>$_2$) 6.55 -7.53 (4H, m, Ar-H)	1650[a]	213 (M$^+$, 46.8) 215 (M$^+$+2, 15.0) 128 (100)
14	**3n**	1.33 (3H, t, *J* = 7.0, C<u>H</u>$_3$-CH$_2$) 2.06 (3H, s, CH$_3$) 4.11 (2H, q, *J* = 7.0, CH$_3$-C<u>H</u>$_2$) 6.80-7.30 (4H, m, Ar-H)	1650[a]	213 (M$^+$, 54.8) 215 (M$^+$+2, 48.4) 128 (100)
15	**4a**	6.07 (2H, brs, NH$_2$) 7.10-8.03 (4H, m, Ar-H)	3330 3250	154 (M$^+$, 100)
16	**4b**	5.87 (2H, brs, NH$_2$) 6.87-7.47 (4H, m, Ar-H)	3330 3270 2230	134 (M$^+$, 100)
17	**4c**	5.87 (2H, brs, NH$_2$) 7.06 (2H, d, *J* = 9.0, Ar-H) 7.43 (2H, d, *J* = 9.0, Ar-H)	3325 3260 2225	134 (M$^+$, 100)
18	**4d**	5.93 (2H, brs, NH$_2$) 6.57-7.33 (3H, m, Ar-H)	3340 3260 2220	152 (M$^+$, 96.8) 108 (100)
19	**4e**	6.00 (2H, brs, NH$_2$) 6.27-7.47 (3H, m, Ar-H)	3350 3250	145(M$^+$, 53.3) 101 (100)
20	**4f**	5.87 (2H, brs, NH$_2$) 6.07-7.30 (3H, m, Ar-H)	3350 3100	145 (M$^+$, 81.6) 101 (100)
21	**4g**	5.95 (2H, brs, NH$_2$) 6.63-7.77 (3H, m, Ar-H)	3350 3270	205 (M$^+$, 71.1) 207 (M$^+$+2, 66.7) 190 (100)

a) Neat.

TABLE 2. continued

Entry	Cmpd	^{1}H NMR (δ)	IR (cm^{-1})	EI-Mass *m/z* (%)
22	**4h**	5.97 (2H, brs, NH_2) 6.87-7.57 (3H, m, Ar-H)	3325 3250	177 (M^+, 43.6) 179 (M^++2, 27.7) 181 (M^++4, 4.6) 161 (100)
23	4i	6.00 (2H, brs, NH_2) 6.78 (1H, dd, *J* = 8.0, 2.0, Ar-H) 7.23 (1H, d, *J* = 8.0, Ar-H) 7.62 (1H, d, *J* = 2.0, Ar-H)	3330 3100	265 (M^+, 50.4) 267 (M^++2, 100) 269 (M^++4, 49.3)
24	**4j**	5.80 (2H, brs, NH_2) 6.27-7.43 (4H, m, Ar-H)	3340[a] 3260	127 (M^+, 84.6) 83 (100)
25	**4k**	5.93 (2H, brs, NH_2) 6.57 -7.63 (4H, m, Ar-H)	3330[a] 3260	127 (M^+, 88.8) 83 (100)
26	**4m**	5.93 (2H, brs, NH_2) 6.50-7.60 (4H, m, Ar-H)	3330 3260	143 (M^+, 56.2) 145 (M^++2, 18.1) 99 (100)

a) Neat.

TABLE 3. Elemental Analyses for New Compounds

Entry	Cmpd	(°C) (solvent)	Elemental Analysis (Found) C	H	N
1	**3a**	43-44 (hexane)	53.57 (53.49)	5.39 (5.49)	12.49 (12.60)
2	**3b**	35-37.5 (pentane)	64.69 (64.43)	5.92 (5.92)	13.72 (13.66)
3	**3d**	48-49 (pet.ether)	59.46 (59.48)	4.99 (5.02)	12.61 (12.49)
4	**3h**	36-36.5 (pet.ether)	48.41 (48.23)	4.47 (4.49)	5.65 (5.65)
5	**3i**	54-55 (hexane)	35.64 (35.61)	3.29 (3.38)	4.16 (4.16)
6	**4a**	56-57 (benzene)	46.76 46.67	3.92 (3.85)	18.18 (18.09)
7	**4b**	67-67.5 (hexane)	62.68 (62.59)	4.51 (4.61)	20.88 (20.75)
8	**4c**	109-110 (benzene)	62.68 (62.66)	4.51 (4.69)	20.88 (20.64)
9	**4d**	84-85 (hexane)	55.27 (55.21)	3.31 (3.41)	18.41 (18.61)
10	**4e**	45.5-46 (hexane)	49.66 (49.76)	3.47 (3.55)	9.65 (9.63)
11	**4f**	111-112 (benzene)[a]	62.65 (62.47)	3.64 (3.76)	5.62 (5.50)
12	**4g**	42-44 (pet.ether)	34.98 (34.95)	2.45 (2.47)	6.80 (6.81)
13	**4h**	79-81 (benzene)	40.48 (40.61)	2.83 (2.89)	7.87 (7.84)
14	**4i**	105-106 (benzene)	27.00 (27.01)	1.89 (1.96)	5.25 (5.00)
15	**4m**	141-143 (benzene)[a]	63.04 (63.02)	4.07 (4.23)	5.66 (5.56)

a) As benzoate.

Typical Procedure. Synthesis of 3,5-Difluorophenoxyamine (4f).- To **3f** (1.34 g, 6.22 mmol) in dioxane (7.5 mL) was added dropwise 70% $HClO_4$ (4.5 mL) with cooling. After stirring the reaction mixture for 1 h at room temperature, it was poured into ice-water (150 mL). The aqueous layer was made alkaline by addition of NaOH pellets with cooling and it was extracted with ethyl acetate (150 mL x 2). The combined organic layer was washed with brine (100 mL), dried over Na_2SO_4, and concentrated. The residue was chromatographed on a column of silica gel with benzene-hexane (2:1) as an eluent to give **4f** (0.59 g, 64%). The spectral data and HRMS are reported in Table 2 and 4.

TABLE 4. HRMS for New Compounds

Entry	Cmpd	Formula	HRMS (found)	
1	**3c**	$C_{11}H_{12}N_2O_2$	204.0899	(204.0909)
2	**3e**	$C_{10}H_{11}F_2NO_2$	215.0758	(215.0773)
3	**3f**	$C_{10}H_{11}F_2NO_2$	215.0758	(215.0775)
4	**3g**	$C_{10}H_{11}BrFNO_2$	274.9957	(274.9954)
5	**3j**	$C_{10}H_{12}FNO_2$	197.0851	(197.0857)
6	**3k**	$C_{10}H_{12}FNO_2$	197.0851	(197.0852)
7	**3l**	$C_{10}H_{12}ClNO_2$	213.0556	(213.0556)
8	**3m**	$C_{10}H_{12}ClNO_2$	213.0556	(213.0556)
9	**3n**	$C_{10}H_{12}ClNO_2$	213.0556	(213.0560)
10	**4j**	C_6H_6FNO	127.0434	(127.0434)
11	**4k**	C_6H_6FNO	127.0434	(127.0434)

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MODIFICATION OF ROUND BOTTOM FLASKS TO ALLOW COMPLETE REMOVAL OF CONTENTS BY SYRINGE

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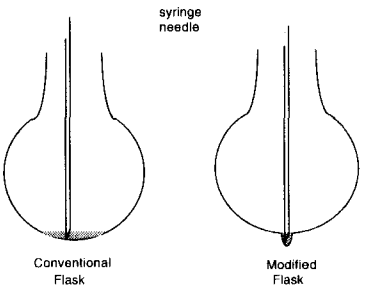
In the course of conducting organic synthesis, transfer of a solution from a flask *via* syringe is often required. If the solution is in a typical round bottom flask, it is virtually impossible to transfer all of the solution using a syringe equipped with a standard needle (the type which are most useful for piercing septa) since when the tip of the needle is on the bottom of the flask, the core of the needle remains a millimeter or so above it. The use of "pear-shaped" flasks greatly improves this situation, though smooth stirring with normal octagonal stir bars is difficult with these flasks. Although special stir bars have been designed to cope with this problem, it would be more convenient if one could use regular octagonal stir bars.



A method of modifying a normal round bottom flask has been developed which alleviates these problems. Though the solution is quite simple, I am unaware of such a modification having been described previously. One simply heats a small spot on the bottom of a round bottom flask using a glassblowing torch, and then, when the glass is soft, a small indentation is made in the bottom of the