A New Synthesis of *N*-Alkoxy-2-ethoxyarylacetamides from *N*-Alkoxy-*N*-chloroarylacetamides with Triethylamine in Ethanol

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Treatment of *N*-alkoxy-*N*-chloroarylacetamides with triethylamine in ethanol results in removal of a chlorine atom and introduction of an ethoxy group at the C-2 position of arylacetamides in moderate yields.

Keywords *N*-alkoxy-*N*-chloroarylacetamide; direct α-ethoxylation; triethylamine; *N*-alkoxyarylacetamide; ethanol

In the course of our investigation of the chemistry of an electron deficient nitrogen atom,[1] we found that removal of a chlorine atom from *N*-alkoxy-*N*-chloroarylacetamides (**2**) with triethylamine in ethanol is coupled to the introduction of the ethoxy group at the C-2 position of *N*-alkoxyarylacetamides (**1**) and gives 2-ethoxy-*N*-alkoxyarylacetamides (**3**) in moderate yields. Recent reports by Hoffman *et al.* on reactions of *O*-sulfonylated hydroxamic acids with nucleophiles[2] have prompted us to publish in detail[3] our results on this related transformation.

Slow addition (over 10 min) of triethylamine to **2** in ethanol is necessary to obtain good results. Reverse addition of **2** causes a considerable decrease in the yield of **3** (in the case of **2a**:**3a**, 14.3%; **6**, 39.2%; **1a**, 31.2%). The use of other bases such as 1,8-diazabicyclo[5.4.0]-7-undecene and sodium ethoxide resulted in formation of the corresponding ethyl ester (**6**) as a main product. In the case of *N*-chloro-*N*-methoxyphenylpropionamide (**2h**), the corresponding ethoxy compound was not obtained at all, but the hydrazine dimer (**5**, 30%) (which was identified by comparison with an authentic sample)[4] and the starting material (**1h**, 50%) was obtained. A radical mechanism is probable because a nitrogen radical could be generated by homolytic cleavage of the N–Cl bond with triethylamine.[5] An aromatic group must be present at C-2 for 2-ethoxylation to occur. Other alcohols such as methanol and isopropanol can be used to produce the corresponding 2-alkoxy compounds (35% and 33%, respectively), while aprotic solvents such as benzene and dichloromethane resulted in the formation of many unidentifiable products.

Alternatively, treatment of **2g** with triethylamine gave only the 2-chloro compound (**4g**). Preferential α-chlorination is attributed to an increase in the acidity of the α-proton by the electron-withdrawing and/or resonance-stabilizing abilities of the nitro substituent (entry 6) or the adjacent carbonyl group (entry 7). A 2-chloro compound is not solvolyzed to the corresponding 2-ethoxy compound under these conditions. Addition of equimolar ethyl 4-methoxyphenylacetate, ethyl phenylacetate or ethyl 4-nitrophenylacetate to the reaction mixture containing **2a** did not affect the yield of **3a** very much (52.6%, 51.7% or 37.6%, respectively). In the last case, chlorination of the additive occurred simultaneously to give a mixture of ethyl 4-nitrophenyl mono- and dichloroacetates in about 20% yield.

TABLE I. Reaction of *N*-Chloro-*N*-alkoxyamides **2** with Triethylamine in Ethanol

Entry	Starting material	Product (%, yield)		
1	**2a**	**3a** (51)		**1a** (19)
2	**2b**	**3b** (59)		**1b** (17)
3	**2c**	**3c** (36)		**1c** (29)
4	**2d**	**3d** (41)		**1d** (24)
5	**2e**	**3e** (38)		**1e** (30)
6	**2f**	**3f** (53)	**4f** (33)	**1f** (4)
7	**2g**		**4g** (67)	

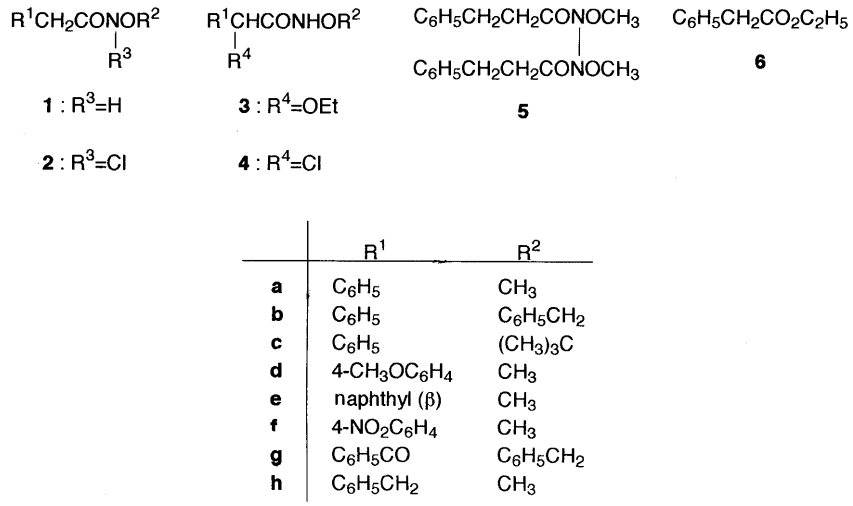

Fig. 1

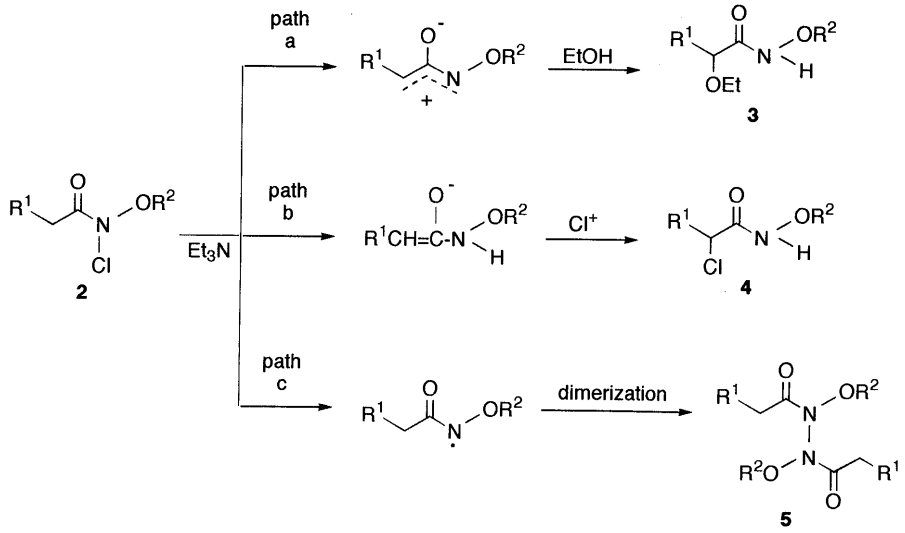

Chart 1

TABLE II. Physical Data for the Products (**3**, **4**, and **5**)

No.	mp (°C) (recryst. solvent)	IR (KBr) ν_{max} cm^{-1} (C=O)	^{1}H-NMR δ (J, Hz)	MS (m/z) M$^+$	Formula	Analysis (%) Calcd (Found) C	H	N
3a	76—77.5 (benzene–hexane)	1670	1.20 (3H, t, 7), 3.50 (2H, q, 7), 3.70 (3H, s), 3.73 (1H, s), 7.30 (5H, s), 9.20 (1H, br s, NH)	—[b]	$C_{11}H_{15}NO_3$	63.14 (63.10	7.23 7.47	6.69 6.75)
3b	76—76.5 (benzene–hexane)	1655	1.34 (3H, t, 7), 3.43 (2H, q, 7), 4.73 (1H, s), 4.83 (2H, s), 7.33 (10H, s), 9.07 (1H, br s, NH)	—[b]	$C_{17}H_{19}NO_3$	71.56 (71.26	6.71 6.80	4.91 5.15)
3c	85—86 (pet.ether)	1670	1.20 (3H, t, 7), 1.23 (12H, s), 3.53 (2H, q, 7), 4.77 (1H, s), 7.30 (5H, s), 8.67 (1H, br s, NH)	—[b]	$C_{14}H_{21}NO_3$	66.90 (66.75	8.42 8.61	5.57 5.43)
3d	Oil	1670[a]	1.20 (3H, t, 7), 3.43 (2H, q, 7), 3.70 (3H, s), 3.73 (3H, s), 4.70 (1H, s), 6.80 (2H, d, 8), 7.27 (2H, d, 8), 9.23 (1H, br s, NH)	239				
3e	89—90 (benzene–hexane)	1670	1.17 (3H, t, 7), 3.42 (2H, q, 7), 3.67 (3H, s), 4.90 (1H, s), 7.27—7.80 (7H, m), 9.43 (1H, br s, NH)	259	$C_{15}H_{17}NO_3$	69.48 (69.49	6.61 6.60	5.40 5.54)
3f	100—101 (benzene–hexane)	1670	1.30 (3H, t, 6), 3.57 (2H, q, 6), 3.73 (3H, s), 4.90 (1H, s), 7.60 (2H, d, 8), 8.23 (2H, d, 8), 9.23 (1H, br s, NH)	254	$C_{11}H_{14}N_2O_5$	51.97 (51.81	5.55 5.62	11.02 11.16)
4f	136—137 (benzene)	1675	3.77 (3H, s), 5.43 (1H, s), 7.63 (2H, d, 8), 8.20 (2H, d, 8), 9.33 (1H, br s, NH)	244 246	$C_9H_9ClN_2O_4$	44.17 (44.15	3.68 3.69	11.45 11.71)
4g	110—111 (benzene)	1660 1700	4.92 (2H, s), 5.65 (1H, s), 7.26—7.67 (8H, m), 7.98—8.01 (2H, d), 9.21 (1H, br s, NH)	303 305	$C_{16}H_{14}ClNO_3$	63.27 (63.36	4.65 4.59	4.61 4.69)
5	Oil	1740[a] 1720[d]	2.40—3.13 (8H, m), 3.62 (6H, s), 7.00—7.57 (10H, m)	164[c]				

a) Neat. *b*) No molecular ion peaks were detected. *c*) Thermal decomposition of **5** gave the corresponding methyl ester (M$^+$ = 164).[4] *d*) Shoulder.

These observations suggest that the conversion of **2** is strongly influenced by the nature of R^1 and the base used, and could take place through one of three processes (Chart 1).

This reaction does not occur with *N*-chloro-*N*-methylphenylacetamide[6] and triethylamine under protection from light (recovery of *N*-methylphenylacetamide 61%), indicating that the *N*-alkoxy moiety plays an important role in the generation and stabilization of a cationic intermediate. *N*-Alkyl-2-alkoxyarylacetamides are obtained from *N*-alkyl-*O*-sulfonylated hydroxamic acids by a somewhat analogous route[2] and 2-alkoxyarylacetates are obtained from arylacetates and hypervalent iodine reagents.[7] Our procedure affords similar transformation in the *N*-alkoxyamide series.

Experimental

Melting points are uncorrected. ^{1}H-NMR spectra were measured at 60 MHz with tetramethylsilane (Me_4Si) as an internal reference and $CDCl_3$ as the solvent. Low-resolution mass spectra (MS) were obtained with a direct inlet system at 70 eV. Elemental analyses were performed in the Microanalytical Laboratory of this University.

Materials Compounds **1a**, **b**, **d**, **e**, **f**, and **h** were prepared according to the literature.[8] Compound **1b**: mp 76.5—77.5 °C ($CHCl_3$–hexane). *Anal.* Calcd for $C_{15}H_{15}NO_2$: C, 74.66; H, 6.27; N, 5.81. Found: C, 74.89; H, 6.45; N, 5.90. Compound **1g** was synthesized from 2-phenyl-1,3-dioxolan-2-acetic acid[9] (mp 91 °C), benzyloxyamine hydrochloride, and triethylamine with dicyclohexylcarbodiimide in CH_2Cl_2, followed by deacetalization, mp 83.5—85 °C (benzene–hexane). *Anal.* Calcd for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.14; H, 5.61; N, 5.33.

***N-tert*-Butoxy-2-phenylacetamide (1c)** A 70% $HClO_4$ solution (0.4 ml) was added dropwise to a mixture of 2-phenylacetohydroxamic acid (1.04 g, 6.86 mmol), *tert*-butyl acetate (7.96 g, 68.6 mmol) and dioxane (30 ml) with stirring at room temperature. Stirring was continued for 2 h, then about half the volume of dioxane was evaporated under reduced pressure, and the residue was diluted with $CHCl_3$ (100 ml). The organic layer was washed with 10% $NaHCO_3$ (30 ml) and brine (30 ml), dried (Na_2SO_4), and concentrated. The crude product was chromatographed on a column of silica gel with AcOEt as the eluent to give *N-tert*-butoxy-2-phenylacetamide (**1c**) (1.24 g, 87.3%), which was recrystallized from benzene–hexane to give

pure **1c** (1.04 g, 73.4%), mp 102.5—104 °C. *Anal.* Calcd for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.63; H, 8.41; N, 6.70.

General Procedure for Preparation of *N*-Alkoxy-2-ethoxyarylacetamides (3) *tert*-Butyl hypochlorite (0.182 ml, 1.53 mmol) was added to a mixture of *N*-benzyloxyphenylacetamide (**1b**) (334.6 mg, 1.39 mmol) and CH_2Cl_2 (3 ml) with cooling. After 20 min, the solvent was evaporated under reduced pressure and the residue was dissolved in ethanol (6 ml). Triethylamine (0.213 ml, 1.53 mmol) in ethanol (1 ml) was added slowly to the ethanol solution with cooling over 7—10 min. After 1 h, the solution was concentrated under reduced pressure and the residue was diluted with CH_2Cl_2 (50 ml). The organic layer was washed with brine (30 ml), dried (Na_2SO_4), and concentrated. The crude products were chromatographed on a column of silica gel with benzene–ethyl acetate (5 : 1) to give *N*-benzyloxy-2-ethoxyphenylacetamide (**3b**) (232.4 mg, 59%) and the starting material (**1b**) (57.3 mg, 17%).

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