THE OXIDATIVE CLEAVAGE OF AMINES BY IODINE MONOCHLORIDE

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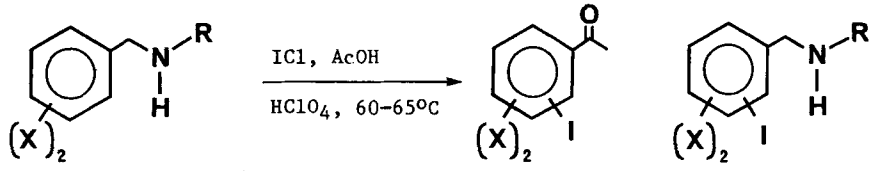
SUMMARY

The formation of secondary products during the radioiodination of aromatic amines is reported. Iodination of a series of N,N-dimethyl-N'-(alkylphenyl)-1,3-propanediamines with ICl in the presence of AcOH and $HClO_4$ gave in addition to the expected iodo derivatives substantially amounts of secondary cleavage products which were identified as the corresponding iodobenzaldehyde derivatives.

Key words: Iodine monochloride; iodination; oxidative cleavage; aromatic amines.

INTRODUCTION

Iodine monochloride (ICl) is a versatile reagent for the iodination and radioiodination of a number of organic substrates including aromatic amines for brain imaging in nuclear medicine [1]. During the course of radioiodination of diamines with ^{125}ICl we observed, in addition to the expected iodo derivatives, the formation of unusual secondary products (15-20%). The reaction was scaled up with nonradioactive ICl which allowed us to identify the secondary products as the corresponding iodobenzaldehydes.



X = OCH_3 and/or CH_3

R = $-(CH_2)_3-N(CH_3)_2$

I = ^{127}I or ^{125}I

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During the past years, several reports have appeared on the cleavage of amines to aldehydes or ketones using a number of reagents or solvent oxidants including aqueous Br_2 [2] or Cl_2 [3], NBS [4,5], IF_5 [6] and DMSO [7], however, the analogous reaction with ICl has not previously been described. ICl has been used as a catalyst for the cleavage of metal-carbon [8], carbon-oxygen [9] and metal-metal [10] bonds.

EXPERIMENTAL

All the melting points are uncorrected. The IR spectra were taken with a Perkin-Elmer mode 457 spectrophotometer. The NMR spectra were recorded on a Varian T60 apparatus. Chemical shifts are reported in δ relative to Me_4Si as an internal standard.

General procedure. To a mixture of N,N-dimethyl-N'-(alkylphenyl)-1,3-propane diamine (1 mmol) in AcOH (6 ml) and $HClO_4$ (70%, 1.5 ml), ICl (1.1 mmol) in AcOH (2 ml) was added dropwise under stirring at room temperature. The temperature was raised to 70-75 °C and stirring was continued for 5 h. The reaction mixture was diluted with water, made alkaline with aqueous NaOH (1N) and extracted with EtOAc. The organic solution was washed with water, dried ($MgSO_4$) and evaporated on a vacuum. The residue was purified by silica gel column chromatography. The corresponding iodobenzaldehydes (15-20%) and iodophenyl diamines (65-70%) were eluted in EtOAc/hexane (1:9) and $MeOH/CH_2Cl_2$ (1:17), respectively. The same protocol using ^{125}ICl gave the corresponding radiolabeled products.

Iodination of benzaldehydes. To the substituted benzaldehyde (1 mmol) in dry $CHCl_3$ (7-10 ml) was added, with stirring, silver trifluoroacetate (1.1 mmol) and thereafter dropwise over 15 min I_2 (1.1 mmol) in $CHCl_3$ (2 ml). After the mixture was stirred for a further 4 h at room temperature, the yellow AgI precipitate was collected by filtration and the filtrate was washed with 5% $NaHSO_3$. After evaporation of the solvent, the residue was chromatographed on a silica gel column in EtOAc/hexane (5:95 - 10:90) to yield the pure iodobenzaldehyde (50-60% yield).

RESULTS

The reaction of ICl in AcOH with N,N-dimethyl-N'(alkylphenyl)-1,3-propanediamines in the presence of $HClO_4$ gave the iodophenyl diamines as a major product (60-65%) together with the corresponding iodobenzaldehyde (15-20%). $HClO_4$ is known to facilitate the iodination [11] and in its absence the reaction predominantly gave non-iodinated products. Aldehyde products were characterized by comparison of their physicochemical properties with those of authentic samples prepared with CF_3COOAg [12] and, when available, with those reported in the literature (Table I). All cleavage products showed the aldehyde absorption band between 1680-1700 cm^{-1} in the IR spectrum and the appropriate molecular ion in the mass spectrum. No cleavage products were obtained when the aromatic ring of the diamine was unsubstituted or substituted with a hydroxyl group only (Table I). Characterization and biological properties of the iodinated diamines will be reported elsewhere.

ACKNOWLEDGEMENTS

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TABLE I. Characterization of substituted benzaldehyde products obtained from the reaction of ICl with various N,N-dimethyl-N'-(alkylphenyl)-1,3-propanediamines.

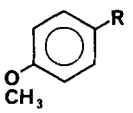
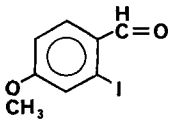
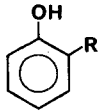
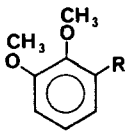
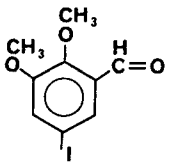
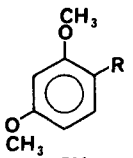
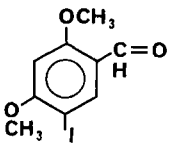
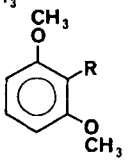
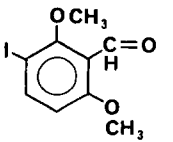
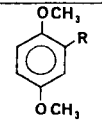
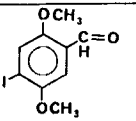
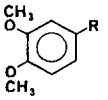
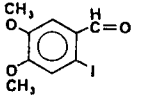
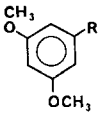
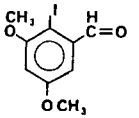
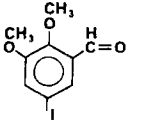
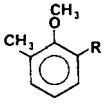
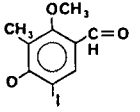
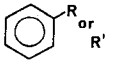
Reactant	Product	mp (°C)	^{1}H NMR ($CDCl_3$) δ*	Ref.
		104.5-6.5	8.13 (d, 1 H, J=2.5 Hz, C_6-H), 7.67 (d, d 1 H, J=8 and 2.5 Hz, C_5-H), 6.77 (d, 1 H, J=8 Hz, C_3H)	13
	No cleavage	---	---	--
		97-98	7.3 (d, 1 H, J=2.5 Hz, C_4-H), 7.62 (d, 1 H, J=2.5 Hz, C_6-H)	--
		172-73	6.3 (s, 1 H, C_3-H), 8.05 (s, 1 H, C_6-H)	--
		48-49	6.53 (d, 1 H, J=8 Hz, ArH), 7.77 (d, 1 H, J=8 Hz, ArH)	--

TABLE I. (Continued)

		135-36	7.03 (s, 1 H, ArH), 7.26 (s, 1 H, ArH)	11
		128-29	7.17 (s, 1 H, ArH), 7.26 (s, 1 H, ArH)	14
		97-98	6.57 (d, 1 H, J=3 Hz, ArH), 6.96 (d, 1 H, J=3 Hz, ArH)	15
		127-28	6.97 (s, 2 H, ArH)	16
		70-71	7.65 (d, 1 H, J=2 Hz, ArH), 7.85 (d, 1 H, J=2 Hz, ArH)	--
	No cleavage	---	---	--

R $CH_2NH-(CH_2)_3N(CH_3)_2$; R' $CH(CH_3)NH(CH_2)_3N(CH_3)_2$.

* All compounds gave characteristic OCH_3 signals between δ 3.8-4.

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