Ruthenium Tetroxide Oxidation of Amines: a New General Synthesis of Amino-acids

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Summary Complex products are obtained from aliphatic primary amines, whilst aniline and its derivatives undergo fragmentation on treatment with ruthenium tetroxide in organic solvents: by conducting the reaction with aralkylamines in acid buffer, controlled oxidation converts the aromatic ring into the carboxyl-residue of an aminoacid.

N-ACYLATED cyclic amines are converted by RuO_4 into lactams,[1] which may also be obtained[2] by oxygenation of the α-methylene group in the 2-phenyl analogues. However, unprotected acyclic amines afford intractable substances although Rylander[3] tentatively assigned an aldehyde and a nitrile as products of the oxidation of 1-aminohexane. We found that 1-aminoheptane formed a polar substance characterised by its i.r. absorption as an imino-compound which was strongly adsorbed from solution in CCl_4, $CHCl_3$, and $MeNO_2$ by the precipitated RuO_2. Oxidation of the periodate complex of 1-aminoheptane[4] with $RuCl_3$ (*ca.* 0·05 equiv.) led to the extraction of the product which on distillation gave 1-cyanohexane[5] (25% yield), b.p. 74° at 26mm Hg, having i.r. and mass spectra[5] identical to those of a reference sample; no volatile carbonyl compounds were detected by g.l.c.[6] Aromatic primary amines undergo fragmentation on treatment with RuO_4 even when a strongly inactivating group is present, as in *p*-nitroaniline.

The amino-group may be protected by *N*-trifluoroacetylation,[7] or alternatively, the amount of free base may be reduced by conducting the oxidation in acidic solution since the tetroxide is stable in cold conc. H_2SO_4 although its solubility is low. Solutions of aromatic amines in H_2SO_4–H_2O (1 : 2 v/v) are rapidly oxidised when in contact with a yellow layer of RuO_4–CCl_4, with discolouration and precipitation of the dioxide. The more basic aliphatic amines[8] are unaffected, even after further dilution with water after several hours exposure to the reagent.

TABLE

Amino-acids obtained by selective oxidation of arylalkylamines with RuO_4

Expt.	Amine	Conditions	Method of characterisation (see text)	Amino-acid (% yield)
1	(I; X=R=H, *n*=0)	24 h; 2°	A	Glycine (66)
2	(I; X=H, R=Me, *n*=0)	16 h; 2°	A	α-Alanine (10)
3	(I; X=OMe, R=Me, *n*=0)	30 min; 10°	A and B	α-Alanine (50)
4	(I; X=OH, R=H, *n*=1)	1 h; 10°	A	β-Alanine (86)
5	(I; X=OH, R=H, *n*=2)	40 min; 10°	B	γ-Aminobutyric (69)
6	Tyrosine	50 min; 10°	B	Aspartic (60)

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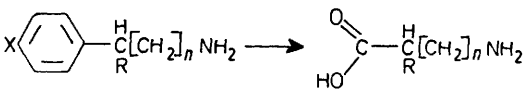
Selective oxidation of substituted amines of type (I) has been demonstrated by using solutions in phosphate buffer at pH 3·0 containing sufficient periodate (12 equiv.)



(I)

to destroy the benzene ring in the presence of $RuCl_3,3H_2O$ (0·02 equiv.) as a catalyst. This method avoids the separation of the amine–periodate complex[4] and adsorption losses are limited by the small amount of dioxide formed. Work up entails removal of insoluble iodate and elution of the salt-free amino-acid from a Dowex 50W column[9] with 4N-ammonia solution with final freeze-drying of the ammonia-free evaporate. The yields quoted (Table) are for crude materials (II) which were characterised either (method A) by sublimation[10] and comparison of their infrared adsorption and R_f values with standard compounds, or (method B) by comparison of the g.l.c.–mass spectral data of their *N*-trifluoroacetyl esters[11] with those of standards.

The method is general since typical α-, β-, and γ-amino-acids have been obtained. A precursor bearing an electron-donating substituent in the aromatic ring is preferable as it enhances the rate of ring cleavage; thus a poor yield of α-alanine from α-phenylethylamine (expt. 2) is much improved when the 4-methoxy-analogue is used (expt. 3). The latter precursor was obtained by reduction of the ketoxime; this indicates a potential use for the high-yield synthesis of labelled amino-acids. Interconversion of amino-acids, which are not themselves oxidised under the conditions, is illustrated by the formation of aspartic acid (expt. 6). It should be noted that preferential oxidation of the inactivated benzene ring (expt. 1) in the acid buffer contrasts with its survival during the oxidation[2] of 2-phenyl-*N*-acetylpyrrolidines and piperidines.

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