α-Amination of Carboxylic Acids: a New Synthesis of α-Amino-acids

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Summary Amination of α-lithiated carboxylic acid salts provides a new preparative method of α-amino-acids.

WE report a new method for the synthesis of α-amino-acids by the amination of α-lithiated acid salts[1] [see reaction (1)].

$$RCH_2CO_2H \xrightarrow{LiNPr^i_2} RCH(Li)CO_2Li \xrightarrow{NH_2X} RCH(NH_2)CO_2H \quad (1)$$

For example, phenylacetic acid was lithiated in tetrahydrofuran–hexane using hexamethylphosphoramide as co-solvent,[2] and treated with *O*-methylhydroxylamine at *ca.* − 15° for 2 h. After work-up, α-phenylglycine† was obtained in 55·5% yield, with 32·8% recovery of the starting acid.

Isovaleric acid was aminated under the same conditions to give valine† in 33·9% yield. In an attempt to improve the yield, several aminating reagents were investigated:‡ *O*-ethylhydroxylamine (22·2%), *O*-isopropylhydroxylamine (25·4%), *O*-t-butylhydroxylamine (18·3%), *O*-benzylhydroxylamine (trace), chloramine (7·7%), *O*-mesitoylhydroxylamine (4·3%), *O*-(3,5-dinitromesitoyl)hydroxylamine§ (5·3%), and hydroxylamine *O*-sulphonic acid (trace).

This is the first method reported for the preparation of α-amino-acids from carboxylic acids by a one stage procedure. Application of the method to the synthesis of other amino-acids is under way.

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† Racemic form.

‡ Yields were determined by an amino-acid analyser. We thank Drs. Y. Ogihara and T. Tanimura for the measurement.

§ M.p. 150—153° (decomp.), prepared from mesitoic acid by successive treatment with fuming nitric acid, thionyl chloride, t-butyl *N*-hydroxycarbamate, and hydrogen chloride.

[1] *Cf.* P. L. Creger, *J. Amer. Chem. Soc.*, 1967, **89**, 2500; 1970, **92**, 1396, 1397; G. W. Moersch and A. R. Burkett, *J. Org. Chem.*, 1971, **36**, 1149.

[2] P. E. Pfeffer and L. S. Silbert, *J. Org. Chem.*, 1970, **35**, 262; P. E. Pfeffer and L. S. Silbert, *Tetrahedron Letters*, 1970, 699.