Reductive Radical Decarboxylation of Amino-acids and Peptides

Derek H. R. Barton, Yolande Hervé, Pierre Potier, and Josiane Thierry*

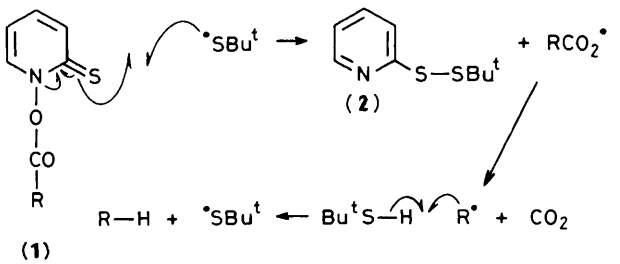
Institut de Chimie des Substances Naturelles, C.N.R.S., 91190 Gif-sur-Yvette, France

Radicals generated from *N*-protected α-amino-acids by photolysis of their *N*-hydroxypyridine-2-thione esters at room temperature are efficiently quenched by t-butyl thiol to give decarboxy-acids; comparable reactions have been carried out on the side chain carboxy groups of suitably protected aspartic and glutamic acids.

In a recent article[1] it was reported that esters (**1**) of *N*-hydroxypyridine-2-thione provided a controlled source of carbon radicals. By the addition of a hydrogen atom transfer reagent, like t-butyl thiol, a radical chain reaction could be set up to give the reduced nor-acid (Scheme 1) in good yield. Since esters of type (**1**) are not electrophilic, as are normal Hunsdiecker intermediates, this decarboxylation process is compatible with many functional groups that otherwise would need protection.

We considered that decarboxylation of amino-acids and peptides should be a process amenable to this new type of radical chemistry.

We first examined (Table 1) the decarboxylation of *N*-protected α-amino-acids. A convenient procedure was to form the mixed anhydride of the *N*-protected amino-acid at −15 °C in tetrahydrofuran using isobutyl chlorocarbonate and *N*-methylmorpholine (1 equiv.) with stirring for 5 min. The *N*-hydroxypyridinethione and triethylamine were then added and the stirring continued for 15 min at −15 °C. After addition of t-butyl thiol (10 mol. equiv.) the solution was irradiated at room temperature with two 100 W tungsten lamps until the ester had disappeared (10—20 min for 1 mmol.). Workup by standard techniques afforded with good yields (Table 1) the decarboxylated amino-acids. The expected[1] disulphide (**2**) was also formed in good yield. Noteworthy is the fact that indolic [(**9**)], hydroxylic [(**11**), (**13**)] and phenolic [(**15**)] functions did *not* need any protection in this procedure.



Scheme 1

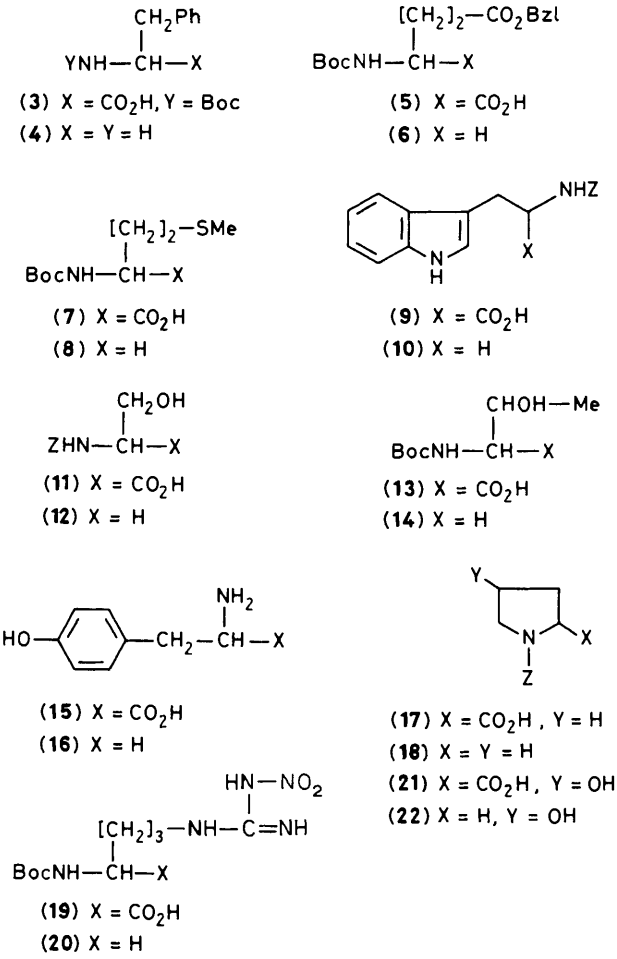


Table 1.[a] Decarboxylation of *N*-protected α-amino-acids.

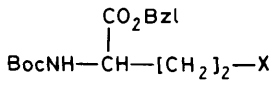
Starting material	Product isolated	Yield (%)	Characterisation
(**3**)	(**4**)[b]	85	Comparison with authentic specimen
(**5**)	(**6**)	93	M.p. 64 °C (EtOAc–cyclohexane)[c]
(**7**)	(**8**)	78	Oil
(**9**)	(**10**)	96	M.p. 85.5 °C (EtOAc–pentane)
(**11**)	(**12**)	79	M.p. 61 °C (EtOAc–cyclohexane)
(**13**)	(**14**)	87	$[\alpha]_D$ −15° (*c* 1.1, MeOH)
(**15**)	(**16**)	96	M.p. 100 °C (Et_2O–cyclohexane)
(**17**)	(**18**)	81	
(**19**)	(**20**)	80	M.p. 109 °C (EtOAc–cyclohexane)
(**21**)	(**22**)	79	M.p. 58 °C $[\alpha]_D$ −15° (*c* 0.5, MeOH)
(**36**)	(**37**)	83	M.p. 69–70 °C $[\alpha]_D$ −28° (*c* 1.2, MeOH)

[a] All compounds in Tables 1, 2, and 3 fully characterised by i.r. and n.m.r. spectroscopy and where appropriate, microanalysis. Boc = t-butyloxycarbonyl, Z = benzyloxycarbonyl, Bzl = benzyl. [b] After hydrolysis. [c] Isolated from solvent system shown in parentheses.

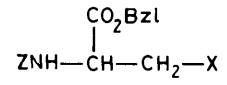
Table 2. Side chain decarboxylation of glutamic and aspartic acid residues.

Starting material	Product isolated	Yield (%)	Characterisation
(**23**)	(**24**)	78	$[\alpha]_D$ −42° (*c* 1.2, MeOH)
(**25**)	(**26**)	48	M.p. 52 °C (Et_2O–cyclohexane), $[\alpha]_D$ −28° (*c* 1.0, MeOH)
(**27**)[a]	(**28**)	78	$[\alpha]_D$ +58° (*c* 0.8, MeOH)
(**29**)[a]	(**30**)	65	M.p. 87 °C (MeOH), $[\alpha]_D$ +63° (*c* 1.0, MeOH)
(**31**)	(**32**)	73	M.p. 126 °C (EtOAc–cyclohexane), $[\alpha]_D$ −35° (*c* 1.0, MeOH)

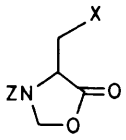
[a] M. Itoh, *Chem. Pharm. Bull.*, 1969, **17**, 1679.



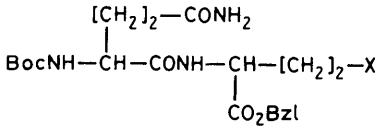
(23) X = CO_2H
(24) X = H
(34) X = Br



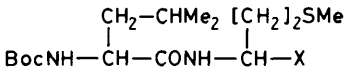
(25) X = CH_2—CO_2H
(26) X = Me
(35) X = CH_2Br



(27) X = CH_2CO_2H
(28) X = Me
(29) X = CO_2H
(30) X = H
(33) X = CH_2Br



(31) X = CO_2H
(32) X = H



(36) X = CO_2H
(37) X = H

We have also examined the applicability of this radical chemistry to the side chain carboxy groups of glutamic and aspartic acid residues (Table 2). The yields of decarboxylated products were satisfactory but, as expected from relative radical stabilities, the side chain decarboxylation is less facile than the α-amino-acid decarboxylation.

Recent interest[2] in the synthesis of modified amino-acids using organocopper chemistry demonstrates the importance of a convenient method of conversion of side chain carboxy into bromide or iodide. We have already shown the facility with which this Hunsdiecker chemistry can be effected[3] using esters of type (**1**). We now report (Table 3) the first utilisation for the side chain carboxy groups of amino-acids. The yields obtained are reasonable and suggest many potential manipulations of peptide side chains.

Table 3. Conversion of side chain carboxy into bromide in amino-acids.

Starting material	Product isolated	Yield (%)	Characterisation
(27)	(33)	73	M.p. 66.5 °C (cyclohexane) $[\alpha]_D$ +54° (*c* 0.9, MeOH)
(23)	(34)	64	M.p. 53 °C (pentane) $[\alpha]_D$ −37° (*c* 1.0, MeOH)
(25)	(35)	64	M.p. 66.5 °C (Et_2O–cyclohexane) $[\alpha]_D$ −37° (*c* 1.0, MeOH)

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3 D. H. R. Barton, D. Crich, and W. B. Motherwell, *Tetrahedron Lett.*, 1983, 4979.