101. Preparation of α-Bromo- and α-Chlorocarboxylic Acids from α-Amino Acids[1])

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Summary

Diazotization of α-amino acids in 48:52 (*w/w*) hydrogen fluoride/pyridine along with excess of potassium halide results in the corresponding α-halocarboxylic acids in good to excellent yields *(Table 1* and *2)*.

Pyridinium polyhydrogen fluoride (hydrogen fluoride/pyridine 7:3 (by weight)) a convenient substitute for anhydrous hydrogen fluoride has gained importance in a variety of fluorination reactions, and its application in organic synthesis has been reviewed [2]. Recently we have shown [3] that anchimerically assisted rearrangements observed in the dediazotizative fluorination of α-amino acids with 7:3 (*w/w*) hydrogen fluoride/pyridine reagent is substantially or fully suppressed by using the less acidic 48:52 (*w/w*) hydrogen fluoride/pyridine reagent.

Now we wish to report that diazotization of α-amino acids in the same less acidic media along with excess of potassium halide results in the corresponding α-halocarboxylic acids in good to excellent yields *(Table 1* and *2)*.

Table 1. *Preparation of α-bromocarboxylic acids from α-amino acids*

α-Amino acid	R	Yield[a]) [%]	B.p. [°/Torr][b]) (m.p. [°])	
Alanine	CH_3	77	84–87/1.0	[4]: 65–67/0.5–1.0
α-Aminobutyric acid	C_2H_5	86	95–98/1.0	[4]: 83–86/1.0–1.5
Valine	i-C_3H_7	81	104–108/0.7	[4]: 83–87/1.0–1.5
Phenylalanine	$C_6H_5CH_2$	81	(50)	[5]: (52)
Isoleucine	*sec*-C_4H_9	80	112–115/1.0	[4]: 43–95/0.5–1.0
Threonine	$CH_3CH(OH)$	48	(84–86)	[5]: (87)

[a]) Isolated products showed characteristic IR., ^{1}H-NMR. and ^{13}C-NMR. data.

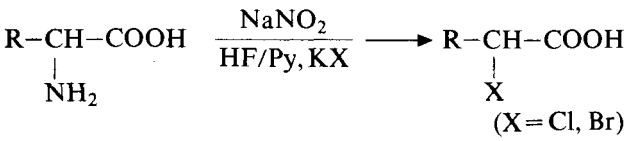
[b]) Boiling and melting points are uncorrected.

[1]) Synthetic Methods and Reactions, Part 117. For Part 116, s. [1].

Table 2. *Preparation of α-chlorocarboxylic acids from α-amino acids*

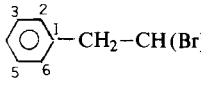
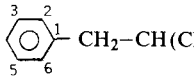
α-Amino acid	R	Yield[a] [%]	B.p. [°/Torr][b] (m.p. [°])	
Alanine	CH_3	74	71–72/0.8	[4]: 49–54/0.5–1.0
α-Aminobutyric acid	C_2H_5	85	88–89/0.7	[4]: 76–78/1.0–2.0
Valine	i-C_3H_7	84	98–99/0.8	[4]: 70–80/1.0–2.0
Phenylalanine	$C_6H_5CH_2$	87	158–159/1.0	[5]: 170–174/2.3–3.5
Isoleucine	sec-C_4H_9	82	105–109/1.0	[4]: 88–90/1.0–2.0
Threonine	$CH_3CH(OH)$	36	(60–64)	[5]: (62–63)

[a]) Isolated products showed characteristic IR., ^{1}H-NMR. and ^{13}C-NMR. data.
[b]) Boiling and melting points are uncorrected.



Whereas the reaction works well with chloride and bromide nucleophiles, with added KI, however, rather complex reaction mixtures are formed, and no pure α-iodocarboxylic acids could be isolated. In the case of tyrosine and added KCl or KBr, a mixture of fluoro and chloro, and fluoro and bromo products, respectively,

Table 3. *^{13}C-NMR. spectroscopic data of α-chloro- and α-bromocarboxylic acids*[a])[b])

α-Haloacid	COOH	C(α)	C(β)	Others
$CH_3CH(Br)COOH$	176.7	39.3	21.3	
$CH_3CH(Cl)COOH$	176.3	52.1	21.3	
$CH_3CH_2CH(Br)COOH$	176.3	46.9	28.0	11.7 (CH_3)
$CH_3CH_2CH(Cl)COOH$	176.1	58.4	28.1	10.3 (CH_3)
$(CH_3)_2CHCH(Br)COOH$	176.0	53.9	32.0	20.0, 19.7 (CH_3[c]))
$(CH_3)_2CHCH(Cl)COOH$	175.8	63.9	32.4	19.5, 17.7 (CH_3[c]))
$CH_3CH_2CH(CH_3)CH(Br)COOH$	175.9	52.4	38.0	26.1 (CH_3CH_2), 16.2 (CH_3CH_2), 10.6 (CH_3)
$CH_3CH_2CH(CH_3)CH(Cl)COOH$	175.9	62.7	38.0	24.8 (CH_3CH_2), 15.9 (CH_3CH_2), 10.8 (CH_3)
	175.6	44.8	40.7	136.3 (C(1)), 129.2 (C(2), C(6)), 128.8 (C(3), C(5)), 127.5 (C(4))
	175.5	57.3	40.8	135.5 (C(1)), 129.4 (C(2), C(6)), 128.7 (C(3), C(5)), 127.5 (C(4))
$CH_3CH(OH)CH(Br)COOH$	173.0	52.3	67.5	20.0 (CH_3)
$CH_3CH(OH)CH(Cl)COOH$	171.2	62.7	68.4	19.4 (CH_3)

[a]) Chemical shifts in ppm from tetramethylsilane.
[b]) In $CDCl_3$ solution at 24°.
[c]) Prochiral.

were obtained. Otherwise the method seems quite general and should find use in the synthesis of α-bromo- or α-chlorocarboxylic acids from readily available α-amino acids.

Experimental Part

Preparation of the reagent. The pyridinium polyhydrogen fluoride (52% pyridine, 48% HF, by weight) was prepared by condensing 73 g (3.85 mol) of anh. HF into 79 g (1 mol) of pyridine at $-78°$ in a polyolefin bottle as previously described [2] or by diluting the reagent HF/pyridine 7:3 with pyridine to achieve the appropriate concentration. *Caution,* sufficient care should be taken while working with this reagent as *HF can cause severe burns* [6].

General procedure for the preparation of α-bromo- or α-chlorocarboxylic acids. To 30 mmol of α-amino acid in 40 ml of above prepared pyridinium polyhydrogen fluoride and 60 mmol of KBr or KCl in a polyolefin bottle with good stirring at r.t. are added 4.14 g (60 mmol) of pre-dried $NaNO_2$ in 4 portions over a period of 10 min. Stirring is continued till the end of the reaction (48 h in the case of bromo and 72 h in the case of chloro acid). Then the mixture is quenched with 100 ml of ice/water and extracted with Et_2O (3 times 100 ml) in a polyolefin separatory funnel. The Et_2O layer is washed with sat. NaCl-solution (3 times 100 ml) and dried over anh. $MgSO_4$. The Et_2O layer on evaporation gives the crude product which is further purified by distillation or recrystallization. In the case of tyrosine and threonine a different workup procedure is employed; the mixture is directly extracted with Et_2O (3 times 100 ml), washed with sat. NaCl-solution (3 times 100 ml), dried over anh. $MgSO_4$ and evaporated to obtain the crude product. – ^{13}C-NMR.: s. *Table 3.*

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