## 101. Preparation of α-Bromo- and α-Chlorocarboxylic Acids from α-Amino Acids<sup>1</sup>)

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## Summary

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

a-Amino acid	R	Yielda) [%]	B.p. [°/Torr] <sup>b</sup> ) (m.p. [°])	
Alanine	CH <sub>3</sub>	77	84-87/1.0	[4]: 65-67/0.5-1.0
a-Aminobutyric acid	$C_2H_5$	86	95-98/1.0	[4]: 83-86/1.0-1.5
Valine	i-C <sub>3</sub> H <sub>7</sub>	81	104-108/0.7	[4]: 83-87/1.0-1.5
Phenylalanine	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>	81	(50)	[5]: (52)
Isoleucine	sec-C <sub>4</sub> H <sub>9</sub>	80	112-115/1.0	[4]: 43-95/0.5-1.0
Threonine	CH <sub>3</sub> CH(OH)	48	(84-86)	[5]: (87)

Table 1. Preparation of a-bromocarboxylic acids from a-amino acids

a) Isolated products showed characteristic IR., <sup>1</sup>H-NMR. and <sup>13</sup>C-NMR. data.

b) Boiling and melting points are uncorrected.

<sup>1)</sup> Synthetic Methods and Reactions, Part 117. For Part 116, s. [1].

α-Amino acid	R	Yielda) [%]	B.p. [°/Torr] <sup>b</sup> ) (m.p. [°])	
Alanine	CH <sub>3</sub>	74	71-72/0.8	[4]: 49-54/0.5-1.0
a-Aminobutyric acid	$C_2H_5$	85	88-89/0.7	[4]: 76-78/1.0-2.0
Valine	i-C <sub>3</sub> H <sub>7</sub>	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 <sub>4</sub> H <sub>9</sub>	82	105-109/1.0	[4]: 88-90/1.0-2.0
Threonine	CH <sub>3</sub> CH(OH)	36	(60-64)	[5]: (62–63)

Table 2. Preparation of a-chlorocarboxylic acids from a-amino acids

$$\begin{array}{ccc} R-CH-COOH & \frac{NaNO_2}{HF/Py, KX} & \longrightarrow & R-CH-COOH \\ & & & \downarrow & & \\ NH_2 & & & X \\ & & & (X=Cl, Br) \end{array}$$

Whereas the reaction works well with chloride and bromide nucleophiles, with added KI, however, rather complex reaction mixtures are formed, and no pure a-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. <sup>13</sup> C-NMR. spectroscopic data of α-chloro- at	nd a-bromocarboxylic acids <sup>a</sup> ) <sup>b</sup> )
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α-Haloacid	COOH	C(a)	$\mathbf{C}(\beta)$	Others
CH <sub>3</sub> CH(Br)COOH	176.7	39.3	21.3	
CH <sub>3</sub> CH(Cl)COOH	176.3	52.1	21.3	
CH <sub>3</sub> CH <sub>2</sub> CH(Br)COOH	176.3	46.9	28.0	11.7 (CH <sub>3</sub> )
CH3CH2CH(Cl)COOH	176.1	58.4	28.1	$10.3 (CH_3)$
(CH <sub>3</sub> ) <sub>2</sub> CHCH(Br)COOH	176.0	53.9	32.0	20.0, 19.7 (CH <sub>3</sub> <sup>c</sup> ))
(CH <sub>3</sub> ) <sub>2</sub> CHCH(Cl)COOH	175.8	63.9	32.4	19.5, 17.7 (CH <sub>3</sub> <sup>c</sup> ))
CH <sub>3</sub> CH <sub>2</sub> CH(CH <sub>3</sub> )CH(Br)COOH	175.9	52.4	38.0	26.1 (CH <sub>3</sub> CH <sub>2</sub> ), 16.2 (CH <sub>3</sub> CH <sub>2</sub> ), 10.6 (CH <sub>3</sub> )
CH <sub>3</sub> CH <sub>2</sub> CH(CH <sub>3</sub> )CH(Cl)COOH	175.9	62.7	38.0	24.8 (CH <sub>3</sub> CH <sub>2</sub> ), 15.9 (CH <sub>3</sub> CH <sub>2</sub> ), 10.8 (CH <sub>3</sub> )
<sup>1</sup> 4 СН <sub>2</sub> —СН(Вг)СООН	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))
$^{4}\sqrt{\sum_{5}^{3}}$ CH <sub>2</sub> -CH(Cl)COOH	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))
CH₃CH(OH)CH(Br)COOH CH₃CH(OH)CH(Cl)COOH	173.0 171.2	52.3 62.7	67.5 68.4	20.0 ( <i>C</i> H <sub>3</sub> ) 19.4 ( <i>C</i> H <sub>3</sub> )

a) Chemical shifts in ppm from tetramethylsilane.

a) Isolated products showed characteristic IR., <sup>1</sup>H-NMR, and <sup>13</sup>C-NMR, data.

b) Boiling and melting points are uncorrected.

b) In CDCl<sub>3</sub> solution at 24°.

c) Prochiral.

were obtained. Otherwise the method seems quite general and should find use in the synthesis of a-bromo- or a-chlorocarboxylic acids from readily available a-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  $-78^{\circ}$  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<sub>2</sub> 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<sub>2</sub>O (3 times 100 ml) in a polyolefin separatory funnel. The Et<sub>2</sub>O layer is washed with sat. NaCl-solution (3 times 100 ml) and dried over anh. MgSO<sub>4</sub>. The Et<sub>2</sub>O 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<sub>2</sub>O (3 times 100 ml), washed with sat. NaCl-solution (3 times 100 ml), dried over anh. MgSO<sub>4</sub> and evaporated to obtain the crude product. - <sup>13</sup>C-NMR.: s. *Table 3*.

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