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α- CHLORINATION AND IODINATION OF ACID CHLORIDES[1]

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We have previously reported that the α-bromination of acid chlorides could be efficiently performed by means of N-bromosuccinimide (NBS)[2]. We have extended our studies in this area and find that acid chlorides can be similarly α-chlorinated <u>and</u> iodinated in excellent yield.

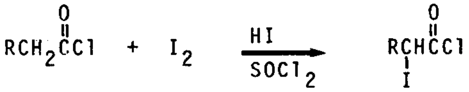
Acid chlorides formed *in situ* by the reaction of the carboxylic acid with $SOCl_2$ react in 2-4 hr with N-chlorosuccinimide (NCS) and a trace of HCl to afford the corresponding α-chloro acid chlorides in 70-87% yield.

A typical procedure is as follows. A mixture of 3-phenyl-propanoic acid (7.51 g, 0.05 mol) and thionyl chloride (14.4 ml, 0.2 mol) was refluxed with vigorous stirring for 0.5 hr. at 75-80°; NCS (16.69 g, 0.125 mol), thionyl chloride (10 ml) and concentrated HCl (8 drops) were then added. The stirring and refluxing were continued and the heating bath was raised to 95°. The reaction was practically complete in 2.0 hr (nmr measurement). After removal of succinimide and solvent, the liquid residue was distilled into a dry ice cooled receiver (short path column) to give 8.51 g (84%) of

2-chloro-3-phenyl-propanoyl chloride, bp 70-71° (0.2 mm) as a clear slightly yellow oil.

N-Chlorosuccinimide proves to be a very useful chlorinating agent since it not only gives good yields of α-chloro products with various types of substrates (Table), but is also selective for protons α to the acyl chloride (i.e. 6 gives 6a). In that respect this method is superior to the Hell-Volhard-Zelinsky (HVZ)[3] reaction (using Cl_2) which leads not only to α-chloro acids, but to chlorination in other chain positions in appreciable amounts[4].

While no direct iodination method for the α-carbon of the acid function appears to have been reported, we find that acid chlorides are cleanly α-iodinated by treatment with molecular iodine and a trace of HI.[5] These

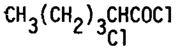
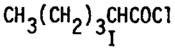
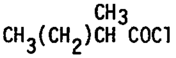
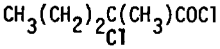
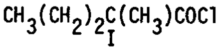
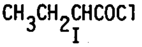
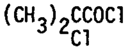
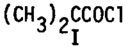
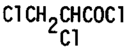
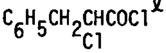
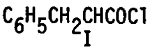
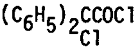


$$\mathrm{RCH_2\overset{\overset{O}{\|}}{C}Cl + I_2 \xrightarrow[SOCl_2]{HI} R\underset{\underset{I}{|}}{C}H\overset{\overset{O}{\|}}{C}Cl}$$

α-iodoacyl chlorides are smoothly transformed into various derivatives under very mild conditions (Table). A typical procedure for the iodination is outlined below.

Hexanoic acid (11.61 g, 0.1 mol), resublimed iodine (15.23 g, 0.12 g atom, and thionyl chloride[6] (40 ml, 0.55 mol) were heated at 130°(bath). Examination of an aliquot by nmr indicated a complete reaction in 1.5 hr. The thionyl chloride was evaporated and excess iodine filtered off. A carbon tetrachloride solution of the residue was shaken with concentrated $Na_2S_2O_3$ to remove the remaining iodine. The organic layer was separated and dried over $MgSO_4$. After solvent evaporation, the product was distilled (62-64°/0.5mm) to yield 21.0 g (80%) of 1b as a water-white liquid.

Table

Compound	Reaction Time (hr)	Temp.[a] o C		Product	bp(°C/mm) mp(°C)	Yield[b] %
$CH_3(CH_2)_4COCl$ 1	1.25	85	1a	 $CH_3(CH_2)_3\underset{Cl}{CH}COCl$ [c]	174-176/760[d]	87
	1.50	130	1b	 $CH_3(CH_2)_3\underset{I}{CH}COCl$	62-64/0.5	80
 $CH_3(CH_2)\overset{CH_3}{CH}COCl$ 2	2.50	85	2a	 $CH_3(CH_2)_2\underset{Cl}{C}(CH_3)COCl$	47-48/1.0	79
	0.75	130	2b	 $CH_3(CH_2)_2\underset{I}{C}(CH_3)COCl$	45-46/0.35	80[e]
$CH_3(CH_2)_2COCl$ 3	1.50	85	3a	 $CH_3CH_2\underset{I}{CH}COCl$ [f]	23/0.1	69
$(CH_3)_2CHCOCl$ 4	2.50	85	4a	 $(CH_3)_2\underset{Cl}{C}COCl$ [g]	58-59/80[h]	70
	0.75	130	4b	 $(CH_3)_2\underset{I}{C}COCl$ [i]	59-60/0.17	80[e]
$ClCH_2CH_2COCl$ 5	2.0	85	5a	 $ClCH_2\underset{Cl}{CH}COCl$ [j]	52-54/16[k]	70
$C_6H_5CH_2CH_2COCl$ 6	2.0	85	6a	 $C_6H_5CH_2\underset{Cl}{CH}COCl$ [ℓ]	70-71/0.2	84
	3.0	130	6b	 $C_6H_5CH_2\underset{I}{CH}COCl$ [m]	83-84/0.5	75
$(C_6H_5)_2CHCOCl$ 7	1.25	85	7a	 $(C_6H_5)_2\underset{Cl}{C}COCl$	52-53[n]	82

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[a] Reaction bath temperature (reaction mixture 85° and 70°)

[b] Yields are based on distilled or recrystallized products; the reactions were complete as per nmr measurement unless stated otherwise. Satisfactory chemical analyses were obtained for all compounds; nmr,ir, and ms properties were consistent with the structures.

[c] amide, mp 56-57°(lit[7a] 57.8-58.2°)

[d] lit[7b] bp 174-176°

[e] The reaction was stopped when α-chloro product started to appear[8]; yield was based on the amount of consumed starting material.

[f] free acid; mp 39-39.5°(lit[7c] 41-42°)

[g] free acid, mp 30-31°(lit[7d] 31°); anilide, mp 67-68°(lit[7e] 67-68°, 69-70°).

[h] lit[7f] bp 126-127°(113-114mm)

[i] anilide, mp 126-126.5°

[j] amide, mp 106-107°(lit[7f] 103°)

[k] lit[7g] 140-144°/720 mm

[ℓ] free acid, mp 48-49°

[m] free acid, mp 74.5-75°

[n] lit[7h] mp 50-51°

The above procedures appear to be quite general in providing a most efficient means of direct α-halogenation. These reactions thus would seem to have considerably wider scope[8] and utility than the HVZ reaction.

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8. When the substrate possesses an α-alkyl or aryl group, the iodination reactions first provide the α-iodo acid chloride which under prolonged heating is converted to the α-chloro acid chloride. Details of this anomaly will be reported in a subsequent article.

ACKNOWLEDGEMENT

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