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of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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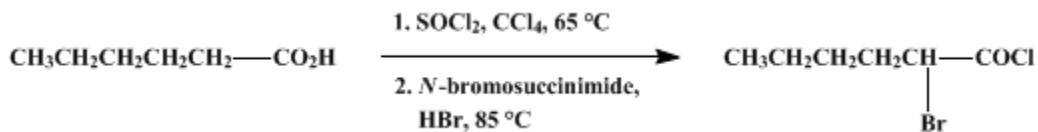
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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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2-BROMOHEXANOYL CHLORIDE



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1. Procedure

Caution! This reaction should be conducted in a good hood since hydrogen chloride and bromine vapors are evolved.

A 200-ml., round-bottomed flask equipped with a magnetic stirring bar is charged with 11.6 g. (0.100 mole) of [hexanoic acid](#) (Note 1) and 10 ml. of [carbon tetrachloride](#). After 46.9 g. (28.8 ml., 0.394 mole) of [thionyl chloride](#) (Note 2) is added to the solution, an efficient reflux condenser with an attached drying tube is fitted to the flask. The solution is stirred and heated with an oil bath at 65° for 30 minutes (Note 3). The flask is removed from the oil bath and cooled to room temperature. To the reaction mixture are added successively 21.4 g. (0.120 mole) of finely powdered [N-bromosuccinimide](#) (Note 4), 50 ml. of [carbon tetrachloride](#), and 7 drops of 48% [hydrogen bromide](#) (Note 5). The flask is heated at 70° for 10 minutes (Note 6), before the temperature of the bath is increased to 85°, until the color of the reaction becomes light yellow (*ca.* 1.5 hours; (Note 7). The reaction mixture is cooled to room temperature, and the [carbon tetrachloride](#) and excess [thionyl chloride](#) are removed under reduced pressure (Note 8). The residue is suction filtered, the solid (Note 9) is washed several times with [carbon tetrachloride](#) (total 20 ml.) and the combined filtrate collected in a 50-ml. flask. The solvent is removed from the solution as before, and the residue is distilled into a dry ice-cooled receiver (short-path column), giving, after a small forerun, 16.1–17.1 g. (76–80%) of [2-bromohexanoyl chloride](#), b.p. 44–47° (1.5 mm.) as a clear, slightly yellow oil, n_D^{22} 1.4707. This material is of sufficient purity for most synthetic purposes (Note 10).

The yellow product (Note 11) is decolorized by dissolving it in an equal volume of [carbon tetrachloride](#) (*ca.* 12 ml.) and vigorously shaking the solution thus obtained with 1.5 ml. of freshly prepared aqueous 35% [sodium thiosulfate](#). The two layers are completely separated after 5 minutes. The colorless bottom layer is drawn off into a 50-ml. Erlenmeyer flask. The top layer is extracted three times with 1.5 ml. of [carbon tetrachloride](#). The combined [carbon tetrachloride](#) extracts are dried over 0.5 g. (Note 12) of anhydrous [magnesium sulfate](#) for 30 minutes. The solution is filtered into a 50-ml. anhydrous [magnesium sulfate](#) for 30 minutes. The solution is filtered into a 50-ml. distilling flask, and the [magnesium sulfate](#) is washed several times with [carbon tetrachloride](#) (total 5 ml.). The solvent is removed, and the colorless product is distilled as described above, affording 14.7–15.8 g. (69–74% overall, based on [hexanoic acid](#); 88–92% for the decolorization step) of colorless [2-bromohexanoyl chloride](#), b.p. 45–47° (1.5 mm.), n_D^{22} 1.4706 (Note 13), d_4^{24} 1.4017 (Note 14) and (Note 15).

2. Notes

1. Practical grade [hexanoic acid](#) is obtainable from Matheson, Coleman and Bell. The submitters report slightly higher yields using purified grade [hexanoic acid](#) obtained from Fisher Scientific Company.
2. [Thionyl chloride](#) was obtained from Anachemia Chemicals Ltd., Fisher Scientific Company (reagent grade), or Matheson, Coleman and Bell. The first two were slightly yellow, and the latter was colorless; however, the yields of final product were identical with each brand. The excess [thionyl chloride](#) serves as a drying agent for the [hexanoic acid](#) and as a solvent for the [N-bromosuccinimide](#), which is not very soluble in [carbon tetrachloride](#).

3. ^1H NMR analysis indicates complete conversion to the acid chloride. This may be monitored by following the disappearance of the triplet ($\text{CH}_2\text{CO}_2\text{H}$) at δ 2.40 and the emergence of a new triplet (CH_2COCl) at δ 2.87.
4. *N*-Bromosuccinimide was obtained from Matheson, Coleman and Bell or Aldrich Chemical Company, Inc. Product yields were optimized using 20% excess, although only 5–10% yield reductions were noted using 5% excess reagent. Recrystallizing the reagent prior to use had no noticeable effect on the overall yield of product.
5. Aqueous 48% hydrogen bromide was obtained from Baker and Adamson. Without added hydrogen bromide, the reaction was much slower.
6. If the reaction was heated too rapidly to 85° , vigorous foaming resulted.
7. Initially the reaction mixture is dark red, and there is bromine vapor in the condenser. Toward the end of the reaction the color lightens considerably and after a short period (*ca.* 15 minutes) begins to darken again. The heat should be removed when this darkening commences. On standing, the yellow solution may also turn black, but the yield of the product is not noticeably affected. When the stirring is stopped, succinimide floats to the top of the solution. The reaction may be conveniently monitored by following the disappearance of the triplet (CH_2COCl) at δ 2.87 and appearance of a triplet (CHBrCOCl) at δ 4.54 in the ^1H NMR spectrum.
8. The evaporation of solvents under reduced pressure should be performed carefully with vigorous stirring at room temperature. An oil pump protected with a dry ice trap and equipped with a manometer is used. Initially the pressure should be adjusted to prevent excessive foaming; it is reduced progressively to approximately 5 mm.
9. About 10 g. of the solid (succinimide) is collected.
10. The IR and ^1H NMR spectra are identical with those of colorless, doubly distilled material; n_D^{22} 1.4706.
11. When the decolorization procedure was carried out before the first distillation, inconsistent yields were obtained. About 2.5 ml. of a dark viscous liquid (giving a violet solution on dilution in carbon tetrachloride) remained in the distillation flask.
12. When more drying agent was employed, the product yield was lower.
13. A central fraction had n_D^{22} 1.4704.
14. Analysis calculated for $\text{C}_6\text{H}_{10}\text{BrClO}$: C, 33.75; H, 4.72; Br, 37.42; Cl, 16.60. Found: C, 33.42; H, 4.77; Br, 37.29; Cl, 16.74. IR (NaCl) cm^{-1} : 2955, 2925, 1785, 1470; ^1H NMR δ (multiplicity, number of protons): 0.94 (m, 3H), 1.43 (m, 4H), 2.10 (m, 2H), 4.54 (t, 1H), mass spectrum m/e : 179, 177 (M–Cl).
15. The corresponding α -bromo acid is prepared by the following procedure. A 500-ml., round-bottomed flask is charged with 10.28 g. (0.04826 mole) of 2-bromohexanoyl chloride and 92 ml. of acetone. The flask is fitted with a magnetic stirring bar, a thermometer, and a 200-ml. dropping funnel in which is placed 115 ml. of aqueous saturated sodium hydrogen carbonate (*ca.* 0.115 mole). The flask is cooled to approximately 10° , while the base is added over a period of about 45 minutes. The mixture is acidified with concentrated hydrochloric acid. An organic layer forms at the top and is separated from the aqueous layer, which is extracted with three 30-ml. portions of chloroform. The combined organic extracts are dried over anhydrous magnesium sulfate and the solvent is removed under reduced pressure, giving 9.36 g. of crude 2-bromohexanoic acid as a colorless liquid. This product is 96% pure by GC analysis, using a Hewlett-Packard 5750 Research Chromatograph with a 1.8 m. 4% SE-30 column at 130° , and having a flow rate of 60 ml./minute. This product can be distilled through a short-path column, yielding, after an 11% forerun, 7.76 g. (83%) of 2-bromohexanoic acid, b.p. $64\text{--}66^\circ$ (0.075 mm.), which shows one peak by GC analysis (as above). IR and ^1H NMR spectra are consistent with the structure.

3. Discussion

The α -bromination of acids (*via* the acid chloride) has been achieved by the Hell–Volhard–Zelinsky reaction or its variances,² however, this technique can involve reaction times of up to 2–3 days,³ high reaction temperatures ($>100^\circ$), copious evolution of hydrogen bromide, and variable yields. A recent procedure,⁴ while affording good overall yields, involves several steps to achieve the transformation (alkylation, proton abstraction, bromination, deacylation and deesterification).

The submitters have found the *N*-bromosuccinimide procedure to be a very general reaction. Alkyl, alicyclic, aryl, and heterocyclic acetic acids have been brominated in 50–80% yield.⁵ The reaction may

be applied in the presence of labile benzylic hydrogens; for example, 3-phenylpropanoic acid gives exclusively 2-bromo-3-phenylpropanoyl chloride.⁶ The procedure has several significant advantages; it is considerably faster than the known methods (overall reaction times of 2 hours are common),⁷ the use of bromine is circumvented, and work-up is simplified considerably.

References and Notes

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

hydrogen chloride,
hydrochloric acid (7647-01-0)

thionyl chloride (7719-09-7)

chloroform (67-66-3)

sodium hydrogen carbonate (144-55-8)

hydrogen bromide (10035-10-6)

bromine (7726-95-6)

carbon tetrachloride (56-23-5)

sodium thiosulfate (7772-98-7)

2-Bromohexanoic acid (616-05-7)

acetone (67-64-1)

hexanoic acid (142-62-1)

3-phenylpropanoic acid (501-52-0)

Succinimide (123-56-8)

magnesium sulfate (7487-88-9)

N-bromosuccinimide (128-08-5)

2-Bromohexanoyl chloride (42768-46-7)

2-bromo-3-phenylpropanoyl chloride