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Working with Hazardous Chemicals

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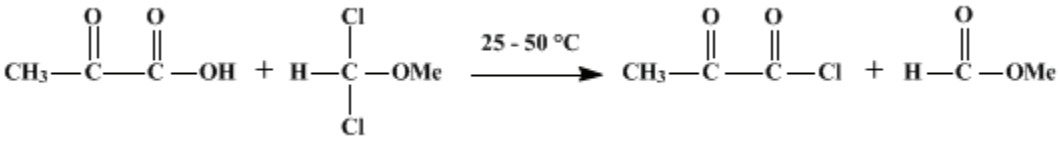
These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

DOI:10.15227/orgsyn.061.0001

Organic Syntheses, Coll. Vol. 7, p.467 (1990); Vol. 61, p.1 (1983).

ACID CHLORIDES FROM α-KETO ACIDS WITH α,α-DICHLOROMETHYL METHYL ETHER: PYRUVOYL CHLORIDE

[Propanoyl chloride, 2-oxo-]



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1. Procedure

A 100-mL, two-necked, round-bottomed flask is equipped with a magnetic stirrer, pressure-equalizing dropping funnel, and a 1.2- × 24-cm vacuum-jacketed Vigreux column that is connected to a condenser, vacuum-take-off adapter, and fraction collector with three receiving flasks (Note 1). The vacuum-take-off adapter is attached to a calcium chloride drying tube which is connected to a water aspirator, and the flask is charged with 35.2 g (28.6 mL, 0.40 mol) of pyruvic acid (Note 2). The pyruvic acid is stirred at room temperature as 46.4 g (36.1 mL, 0.40 mol) of α,α-dichloromethyl methyl ether (Note 3) is added slowly over 30 min. Evolution of hydrogen chloride begins after a few minutes. When the addition is complete, the dropping funnel is removed and replaced by a glass stopper. The solution is stirred and heated at 50°C in an oil bath for 30 min (Note 4) while a few drops of methyl formate are collected as the first fraction (Note 5). The condenser is then cooled to −30°C (Note 6) and the receiving flasks are cooled to −50°C with chilled acetone. The aspirator is turned on and the pressure is adjusted to 190 mm. With the oil bath at 50°C, a second fraction, bp 25–35°C (190 mm), is collected. As soon as the head temperature begins to drop, the pressure is reduced to 120 mm and the temperature of the oil bath is raised slowly to 75°C. A third fraction, bp 35–40°C (120 mm), consisting mainly of pyruvoyl chloride is collected (Note 7) and (Note 8). The second and third fractions are combined to give 33–41 g of a mixture of pyruvoyl chloride and methyl formate, which is redistilled through a 1.4- by 18-cm vacuum-jacketed Vigreux column (Note 1). The condenser and the receiving flasks are cooled to −5°C with chilled acetone. The first fraction, weighing 2.3–11.4 g and consisting mainly of methyl formate, is collected at 25–30°C (190 mm) with an oil bath temperature of 60°C. When the pressure is reduced to 120 mm and the oil bath is maintained at 60°C, 18.6–21.2 g (44–50%) of pyruvoyl chloride, bp 43–45° C (120 mm), distills into the receiver as a light yellow liquid, n_D^{20} 1.4165 (Note 9) and (Note 10).

2. Notes

1. The glassware was dried for 16 hr in an oven at ca. 125°C and assembled while still warm. The checkers used a 27-cm Vigreux column insulated with glass wool instead of the vacuum-jacketed column.
2. Pyruvic acid, supplied by Aldrich Chemical Company, Inc., was freshly distilled: bp 59–62°C (14 mm).
3. α,α-Dichloromethyl methyl ether was purchased from Aldrich Chemical Company, Inc., and redistilled prior to use: bp 83–84°C. The reagent may also be prepared from methyl formate and phosphorus pentachloride.[2] Unlike chloromethyl methyl ether and bis(chloromethyl) ether, α,α-dichloromethyl methyl ether is reported to have no significant carcinogenic activity.[3] However, as a precaution, the compound should be handled with care in a well-ventilated hood.
4. At this temperature the intermediate, chloromethoxymethyl pyruvate, decomposes to pyruvoyl chloride and methyl formate.[4]
5. The submitters made no effort to collect methyl formate quantitatively. The checkers did not observe the formation of any condensate at this point.
6. This was accomplished by the checkers by passing acetone chilled with dry ice slowly through the

condenser jacket. The coolant was contained in a 1-L separatory funnel which was connected to the condenser inlet with a section of Tygon tubing. The effluent was collected in a beaker and periodically returned to the separatory funnel reservoir.

7. Fractions 2 and 3 weighed 10.1–13.4 and 23.6–30.0 g, respectively. Proton NMR spectra of fraction 2 indicated a composition of 70–84% of methyl formate, 16–20% of pyruvoyl chloride, and 0–10% of unreacted starting materials. The composition of fraction 3 was 21–28% of methyl formate, 60–70% of pyruvoyl chloride, and 1–20% of starting materials. The two fractions collected by the checkers boiled at 25–26°C (190 mm) and 40–46°C (120 mm).

8. For some reactions, such as simple esterification, it is not necessary to distill the acid chloride. The crude reaction mixture may be used provided the hydrogen chloride present is neutralized with an appropriate base.[5]

9. The submitters found that pyruvoyl chloride may be stored at −20°C in carbon tetrachloride solution or as the pure liquid in a sealed tube.

10. The product obtained by the checkers boiled at 48–51°C (120 mm) and was contaminated with ca. 5–10% of methyl formate and unreacted starting materials. The spectral properties of the product are as follows: IR (liquid film) cm^{-1}: 2900 (w), 1770 (s, broad), 1415 (m), 1355 (s), 1195 (s), 1130 (m), 1095 (m), 1005 (s), 875 (s); ^1H NMR ($CDCl_3$) δ: 2.51 (s, 3 H). The compound may be characterized as the *p*-nitroanilide derivative.[6]

3. Discussion

Most of the conventional reagents for the synthesis of acid chlorides from carboxylic acids are unsatisfactory for the preparation of α-keto acid chlorides. For example, the reaction of pyruvic acid with phosphorus halides does not give pyruvoyl chloride[7] whereas the use of phosgene[8] or oxalyl chloride[9,10] affords ether solutions of the acid chloride in low yield. Recently a useful preparation of pyruvoyl chloride from trimethylsilyl pyruvate and oxalyl chloride has been described.[11]

The use of α,α-dichloromethyl alkyl ethers for the conversion of carboxylic acids to acid chlorides was first reported by Heslinga et al. in 1957.[4] The submitters have found that the readily available α,α-dichloromethyl methyl ether[2] is the reagent of choice for the preparation of pyruvoyl chloride.[6] This simple and economical procedure has been used in other laboratories,[5,12,13] and the submitters have applied the method to the preparation of three other α-keto acid chlorides: 2-oxobutanoyl chloride (32%), 3-methyl-2-oxobutanoyl chloride (10%), and phenylglyoxylyl chloride (78%).[6]

References and Notes

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

hydrogen chloride (7647-01-0)

ether (60-29-7)

phosphorus pentachloride (10026-13-8)

carbon tetrachloride (56-23-5)

acetone (67-64-1)

phosgene (75-44-5)

methyl formate (107-31-3)

bis(chloromethyl) ether (542-88-1)

chloromethyl methyl ether (107-30-2)

Pyruvic acid (127-17-3)

oxalyl chloride (79-37-8)

phenylglyoxylyl chloride (532-27-4)

α,α-dichloromethyl methyl ether (4885-02-3)

Pyruvoyl chloride,
Propanoyl chloride, 2-oxo- (5704-66-5)

chloromethoxymethyl pyruvate

trimethylsilyl pyruvate

2-oxobutanoyl chloride

3-methyl-2-oxobutanoyl chloride