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of Organic Compounds

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.

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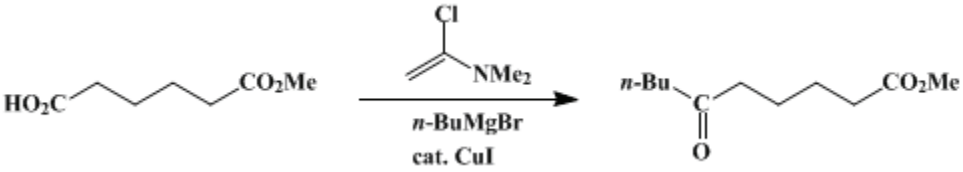
KETONES FROM CARBOXYLIC ACIDS AND GRIGNARD REAGENTS: METHYL 6-OXODECANOATE

[Decanoic acid, 6-oxo-, methyl ester]



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1. Procedure

A 500-mL, three-necked, round-bottomed flask equipped with a magnetic stirring bar, a thermometer, an addition funnel for solids (Note 1), and a rubber septum is flushed with nitrogen. The flask is charged with 50 mL of dichloromethane (Note 2) and 6.92 g (0.052 mol) of 1-chloro-*N*,*N*,2-trimethylpropenylamine (Note 3). The solution is stirred and cooled in an ice bath and 8.01 g (0.050 mol) of adipic acid monomethyl ester (Note 4) is added slowly by means of a syringe over 10 min. After the addition is complete, the cooling bath is removed and the contents of the flask are stirred for 30 min at room temperature (Note 5). The flask is cooled in an ice–salt bath to −15°C. Then 100 mL of tetrahydrofuran (Note 6) and 0.48 g (0.0025 mol) of copper(I) iodide (Note 7) are added to the flask through the septum and the funnel, respectively. To this stirred mixture is added 50.5 mL (0.052 mol) of a 1.03 *M* solution of butylmagnesium bromide (Note 8) in tetrahydrofuran over 1 hr using a syringe pump, while the internal temperature is maintained below −10°C. The reaction mixture is stirred for an additional hour at −15°C. After 100 mL of 2 *M* hydrochloric acid solution has been poured into the flask in one portion, the mixture is transferred to a separatory funnel and the organic layer is separated. The aqueous layer is extracted with two 100-mL portions of hexane. The combined organic extracts are washed with five 10-mL portions of 2 *M* hydrochloric acid solution (Note 9), 100 mL of 5% sodium thiosulfate solution, two 100-mL portions of saturated sodium bicarbonate solution, and 100 mL of brine, dried over anhydrous sodium sulfate, and filtered. The solvent is evaporated under reduced pressure and the residual liquid is distilled with a short-necked Claisen distillation flask. After separation of a small forerun (<0.3 g) (Note 10), 8.53–8.67 g (85–86%) of methyl 6-oxodecanoate is collected, bp 106–110°C (2.8 mm) (Note 11).

2. Notes

1. A simple bent glass tube is useful as an addition funnel for copper (I) iodide.
2. Dichloromethane was distilled over calcium hydride, and stored over Linde 4A molecular sieves.
3. *N*,*N*-Dimethylisobutyramide (Gavrilov, N.; Koperina, A.; Klutcharova, M. *Bull. Soc. Chim. Fr.* **1945**, *12*, 773) was converted to 1-chloro-*N*,*N*,2-trimethylpropenylamine according to the procedure of *Org. Synth., Coll. Vol. VI*, **1988**, 282, in 61% yield, bp 118–121°C. Freshly distilled oxalyl chloride was used instead of phosgene. The propenylamine should be handled carefully in a syringe to avoid its rapid hydrolysis by moisture.
4. Adipic acid monomethyl ester was purchased from Nakarai Chemicals or Aldrich Chemical Company, Inc. and distilled before use, bp 155–158°C (7 mm).
5. In a separate experiment, formation of adipic acid monomethyl ester monochloride was observed.[2]
6. Tetrahydrofuran was freshly distilled from the sodium ketyl of benzophenone.
7. Copper(I) iodide purchased from Wako Chemicals was used without purification.
8. Butylmagnesium bromide was prepared from magnesium and butyl bromide in tetrahydrofuran at room temperature by a standard procedure (*Org. Synth., Coll. Vol. VI*, **1988**, 407), and titrated by the procedure of Watson and Eastham.[3]

9. The organic extracts must be washed 4 or 5 times to remove *N,N*-dimethylisobutyramide.
10. The forerun consisted of *N,N*-dimethylisobutyramide, other by-products, and methyl 6-oxodecanoate.
11. The reported physical constants are bp 149°C (13.5 mm),[4] 97–103°C (3.5 mm),[5] n_D^{20} 1.4377,[4] n_D^{25} 14376.[5] Gas-chromatographic analysis of the product using a 3 mm × 1-m stainless-steel column, 15% SE-30 on 60–80-mesh Chromosorb W (AW), 150°C, 50 mL of nitrogen per minute indicated a purity of 99.6% (the retention time is 6.9 min). The spectral properties of the product are as follows: IR (liquid film) cm^{-1}: 2960, 2870, 1740, 1714, 1454, 1435, 1415, 1370, 1200, 1175; ^1H NMR (60 MHz, CCl_4) δ: 0.9 (t, 3 H, $J = 7$, CH_3), 1.06–1.86 (m, 8 H, CH_2), 2.06–2.56 (m, 6 H, $CH_2C{=}O$), 3.60 (s, 3 H, OCH_3).

3. Discussion

The direct coupling of Grignard reagents with carboxylic acids is not generally useful for ketone synthesis because of the accompanying formation of tertiary alcohols. An exception is the recently published method using a nickel catalyst.[6] In order to accomplish such a chemoselective ketone synthesis, the method of activation of carboxylic acid in situ is important, and several activating reagents have been proposed for the purpose, such as a bulky acyl chloride,[7] dichlorotriphenylphosphorane,[8] or *N,N*-diphenyl-*p*-methoxyphenylchloromethylenammonium chloride,[9] which react with carboxylic acids to produce mixed anhydrides, carboxyphosphonium salts, or carboxymethylenammonium salts, respectively.

The present procedure, reported earlier by the submitters,[10] illustrates a general method for ketone synthesis in a one-pot operation using an α-chloroenamine as a condensation reagent. 1-Chloro-*N,N*,2-trimethylpropenylamine reacts with carboxylic acids to produce the corresponding acyl chlorides,[2] which instantaneously couple with Grignard reagents in the presence of a copper catalyst to give ketones. The utility of the procedure is as follows: (a) an equimolecular amount of Grignard reagent is sufficient to complete the reaction of carboxylic acid and (b) the exceptionally high chemoselectivity of the reaction tolerates various kinds of functional groups such as nitrile, halide, ester and even ketone.[10]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 8, 498

References and Notes

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

brine

sodium ketyl of benzophenone

Adipic acid monomethyl ester monochloride

α-chloroenamine

hydrochloric acid (7647-01-0)

sodium bicarbonate (144-55-8)

magnesium (7439-95-4)

Butyl bromide (109-65-9)

sodium sulfate (7757-82-6)

sodium thiosulfate (7772-98-7)

nitrogen (7727-37-9)

copper (7440-50-8)

nickel (7440-02-0)

phosgene (75-44-5)

Butylmagnesium bromide (693-03-8)

dichloromethane (75-09-2)

copper(I) iodide,
copper (I) iodide (7681-65-4)

Tetrahydrofuran (109-99-9)

oxalyl chloride (79-37-8)

hexane (110-54-3)

adipic acid monomethyl ester (627-91-8)

calcium hydride (7789-78-8)

Dichlorotriphenylphosphorane (2526-64-9)

Methyl 6-oxodecanoate,
Decanoic acid, 6-oxo-, methyl ester (61820-00-6)

1-Chloro-N,N,2-trimethylpropenylamine (26189-59-3)

N,N-dimethylisobutyramide (21678-37-5)

N,N-diphenyl-p-methoxyphenylchloromethylenammonium chloride