Organic Syntheses

A Publication
of Reliable Methods
for the Preparation
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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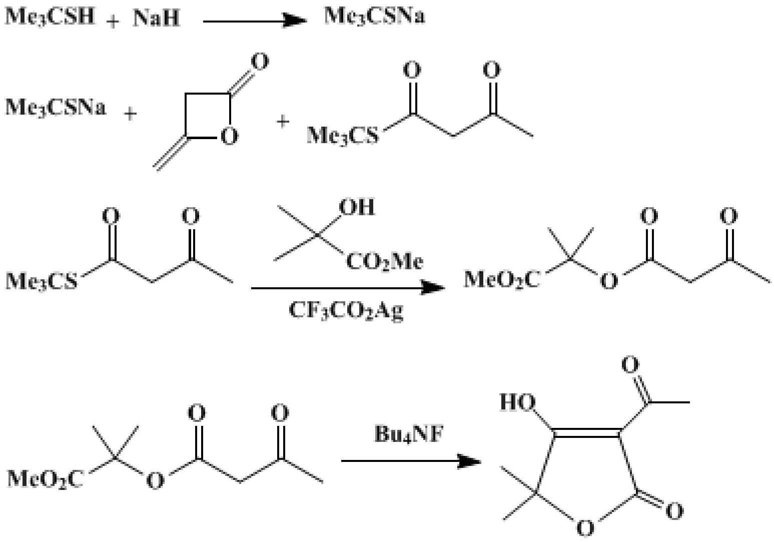
tert-BUTYL ACETOTHIOACETATE AND ITS USE IN SYNTHESIS: 3-ACETYL-4-HYDROXY-5,5-DIMETHYLFURAN-2(4*H*)-ONE

[Acetoacetic acid, 1-thio-, *S*-*tert*-butyl ester]



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1. Procedure

Caution! 2-Methylpropane-2-thiol should be handled in an efficient fume hood because of its odor.

A. *S-tert-Butyl 3-oxobutanthioate.* A dry, 2-L, three-necked, round-bottomed flask (Note 1) fitted with a 100-mL pressure-equalizing dropping funnel, a thermometer, a magnetic stirring bar, and an argon inlet is charged with 9.8 g (0.24 mol) of sodium hydride as a 60% dispersion in oil (Note 2). The system is flushed with, and kept under, dry argon. The sodium hydride is washed with two 40-mL portions of sodium-dried pentane and the system is purged with dry argon to remove traces of pentane. To the flask is then added 900 mL of dry tetrahydrofuran (Note 3).

The flask is cooled in an ice–salt bath to −5°C and a solution of 20 g (25 mL, 0.22 mol) of 2-methylpropane-2-thiol (Note 2) in 20 mL of dry tetrahydrofuran is added at such a rate as to maintain a steady evolution of hydrogen. The slightly exothermic reaction causes the temperature to rise to 0°C and the colorless solution is stirred at this temperature for 15 min to ensure complete formation of the thiolate. The reaction mixture is then recooled to −5°C and 20.3 g (18.8 mL, 0.24 mol) of diketene (Note 2) is added over 15 min to give a yellow-green solution. The cooling bath is removed and the solution allowed to warm to room temperature.

The reaction is quenched and excess sodium hydride is destroyed by careful addition of 300 mL of saturated ammonium chloride solution. The two-phase mixture is transferred to a 2-L separatory funnel charged with 400 mL of ether. The layers are separated and the organic phase is washed with 300-mL portions of water, saturated sodium bicarbonate solution, and Brine. The aqueous washes are reextracted with a 400-mL portion of ether and the combined organic layers are dried over anhydrous sodium sulfate. The solvent is removed with a rotary evaporator to give the crude product as a deep-red oil. Bulb-to-bulb distillation (Note 4) at 95–100°C (0.9 mm) gives 22 g (57%) of *S-tert*-butyl 3-oxobutanthioate as a colorless oil (Note 5).

B. *1-Carbomethoxy-1-methylethyl 3-oxobutanoate.* A 500-mL, round-bottomed flask equipped with a magnetic stirring bar is charged with 10 g (0.085 mol) of methyl 2-hydroxyisobutyrate (Note 2), 17.7 g (0.102 mol) of *S-tert*-butyl 3-oxobutanthioate, and 250 mL of dry tetrahydrofuran. The flask is placed in the dark and 22.5 g (0.102 mol) of freshly prepared silver(I) trifluoroacetate (Note 6) is added in two portions. The resulting dark-brown suspension is stirred for 15 min (Note 7) and then concentrated to approximately 50 mL with a rotary evaporator. The concentrated mixture is diluted with 200 mL of hexane and the resulting orange-brown precipitate is removed by filtration. The filtered solid is washed with two 50-mL portions of hexane and the combined filtrate and washings concentrated with a rotary evaporator to give an orange-brown oil.

The crude product is chromatographed on 350 g of silica (Note 8) using 1 : 1 ether-petroleum ether (40–60) as eluant. The chromatography is monitored by TLC (Note 9) and the appropriate fractions are combined. Removal of the solvent with a rotary evaporator gives a pale-orange oil (Note 10), which was further purified by distillation to give 11.7 g (68%) of the *O*-ester, bp 69–72°C (0.2 mm) (Note 11).

C. *3-Acetyl-4-hydroxy-5,5-dimethylfuran-2(5H)-one.* A 100-mL, round-bottomed flask equipped with a 50-mL pressure-equalizing dropping funnel and a magnetic stirring bar is charged with 5 g (0.025 mol) of the acetoacetate and 37 mL (0.037 mol) of tetrabutylammonium fluoride (1 *M* solution in THF) (Note 2) is added over 5 min. The resulting solution is stirred vigorously for 3 hr (Note 12) and then transferred to a 250-mL separatory funnel containing 50 mL of 6 *M* hydrochloric acid. The acidified mixture is extracted with three 30-mL portions of ether, each extract being washed with 10 mL of Brine. The combined organic extracts are dried over anhydrous sodium sulfate and concentrated with a rotary evaporator to give 4.3 g of the crude tetronic acid as a yellow solid. Recrystallization from 25 mL of hot 5% ether–petroleum ether gives 1.9 g of the tetronic acid as pale-yellow plates, mp 66–67°C (lit.[2]: mp 64–65°C) (Note 13). Concentration of the mother liquor affords a second crop of 0.4 g, mp 63–65°C, giving a combined yield of 54%.

2. Notes

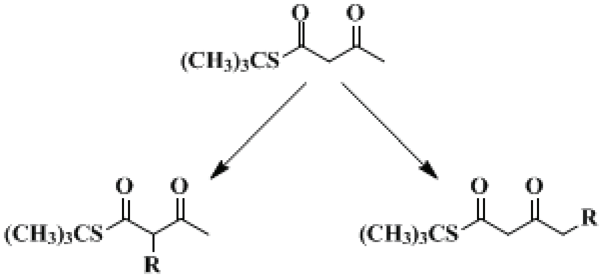
1. The apparatus was oven-dried, assembled while hot, and cooled under a stream of dry argon.
2. Sodium hydride, 2-methylpropane-2-thiol, diketene, methyl 2-hydroxyisobutyrate, and tetrabutylammonium fluoride were purchased from Aldrich Chemical Company, Inc. Diketene was distilled prior to use to remove polymeric species.
3. Tetrahydrofuran was refluxed over and distilled from sodium/benzophenone immediately prior to use.
4. A Kugelrohr apparatus was used for the distillation. The reported temperature is the oven temperature.
5. The checkers found that the yield of this material was substantially higher (83%) when the reaction was conducted at ¼ scale. Spectral properties of the product[3] [4] are as follows: IR (neat) cm^{-1}: 1712, 1676, 1621; ^{1}H NMR (60 MHz, $CDCl_3$) δ: 1.5 (s, 9 H, $(CH_3)_3C$), 2.3 (s, 3 H, $COCH_3$), 3.6 (s, 2 H, $COCH_2CO$), 5.3 (s, COCH=C(OH)).
6. Silver(I) trifluoroacetate may be obtained commercially, but it is recommended that it be freshly prepared.[5] Trifluoracetic acid (18 mL, 0.24 mol) is added to silver(I) oxide (0.12 mol), freshly precipitated from silver nitrate (20 g, 0.12 mol) and sodium hydroxide (4.7 g, 0.12 mol) in water (30 mL). The solution is filtered and evaporated to dryness under reduced pressure. The crude product is purified by dissolving it in ether (150 mL), filtering through decolorizing charcoal and evaporation to give the product as a white crystalline solid (19.3 g, 74%).
7. The time reported represents the average reaction time. The reaction can be followed by TLC, visualizing with iodine and 10% phosphomolybdic acid in ethanol followed by heating on a hot plate.
8. Merck Kieselgel 60 silica gel (230–400 mesh) was used.
9. Merck precoated silica gel 60 F-254 plates were used, visualizing with iodine.
10. In some cases, the product is contaminated with a yellow solid even after chromatography. This is removed prior to distillation by filtering through a short pad of Celite.
11. The spectral properties of the product[2] are as follows: IR (neat) cm^{-1}: 1745, 1720; ^{1}H NMR δ (90 MHz, $CDCl_3$): 1.57 (s, 6 H, $(CH_3)_2C$), 2.28 (s, 3 H, $COCH_3$), 3.44 (s, 2 H, $COCH_2CO$), 3.72 (s, 3 H, CO_2CH_3).
12. The reaction is monitored by TLC and quenched when starting material has been consumed.

13. Spectral properties of the product[2] are as follows: IR (KBr) cm^{-1}: 1758, 1685, 1610; ^{1}H NMR (60 MHz, $CDCl_3$) δ: 1.50 and 1.51 [2 s, 6 H, $C(CH_3)_2$], 2.5 (s, 3 H, $COCH_3$), 9.25 (br s, 1 H, OH).

3. Discussion

Selective alkylation of β-keto esters via either anions or dianions is an important synthetic transformation.[6] Equally, thioesters may be transesterified in the presence of thiophilic metal cations.[7] These two features can be usefully combined in one substrate, *tert*-butyl acetothioacetate, the subject of this Organic Syntheses procedure.

Alkylation at the 2-position can be achieved by formation of the anion with sodium hydride in 1,2-dimethyoxyethane (DME) at 0°C followed by reaction with an alkyl halide at room temperature. Alternatively, selective alkylation at C-4 involves sequential treatment with sodium hydride (at −10°C) and butyllithium in DME (at −40°C) to form the dianion, followed by kinetic alkylation with an alkyl halide (or carbonyl compound).[8]



The choice of DME as solvent in these reactions is important as other ether solvents are much less successful and lead to unwanted side products.

Transesterification of the resulting alkylated β-keto thioesters to the corresponding oxo esters is readily achieved using alcohols under various metal catalysis.[7]

The alcohols used may also contain fairly sensitive functional groups, such as esters, halides, and silyl ethers. In this work, therefore, *tert*-butyl acetothioacetate is behaving as a synthetic equivalent to diketene. When this methodology is used, it is possible to devise very short syntheses of acyl tetronic acids[8] and novel macrocyclic structures.[9]

References and Notes

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Appendix

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

petroleum ether

brine

1,2-dimethyoxyethane

sodium/benzophenone

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

ether (60-29-7)

ammonium chloride (12125-02-9)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

sodium bicarbonate (144-55-8)

silver(I) oxide (20667-12-3)

silver nitrate (7761-88-8)

sodium sulfate (7757-82-6)

iodine (7553-56-2)

diketene (674-82-8)

Pentane (109-66-0)

acetoacetate

butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

sodium hydride (7646-69-7)

hexane (110-54-3)

argon (7440-37-1)

Trifluoracetic acid (76-05-1)

silver(I) trifluoroacetate (2966-50-9)

phosphomolybdic acid (51429-74-4)

Tetrabutylammonium fluoride (429-41-4)

2-methylpropane-2-thiol (75-66-1)

methyl 2-hydroxyisobutyrate (2110-78-3)

tetronic acid (4971-56-6)

tert-BUTYL ACETOTHIOACETATE

3-ACETYL-4-HYDROXY-5,5-DIMETHYLFURAN-2(4H)-ONE

S-tert-butyl 3-oxobutanthioate (15925-47-0)

1-Carbomethoxy-1-methylethyl 3-oxobutanoate (110451-07-5)

3-Acetyl-4-hydroxy-5,5-dimethylfuran-2(5H)-one (22609-93-4)

Acetoacetic acid, 1-thio-, S-tert-butyl ester