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AN IMPROVED MULTIGRAM-SCALE PREPARATION OF S-TERTBUTYL ACETOTHIOACETATE.

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<u>Abstract</u>: An efficient synthesis of S-tertbutylacetothioacetate was achieved by reaction between ^tbutylthiol and 2,2,6-trimethyl-4H-1,3-dioxin-4-one.

Acetoacetylation of nucleophillic atoms, although seemingly trivial, is a very important synthetic transformation. Diketene¹ is one of the most commonly employed acetoacetylating agents, but it suffers from many disadvantages due to its low stability and high volatility and toxicity, and also to the fact that it is not readily transformed into its substituted derivatives. Among diketene equivalents, *S*-*tert*butyl acetothioacetate has proved to be particularly valuable, as it combines two very useful properties, namely regioselective alkylation at C₂ or C₄² and easy transformation into esters² and amides³. Therefore, this compound has served as a building block in several concise, elegant syntheses of some acyl tetronic acid-related natural products⁴ and a variety of novel macrocycles⁵, among other accomplishments.

2329

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SCHEME I

The methods available for the preparation of β -ketothioesters are limited in their scope, and generally not high yielding. Thus, in the best synthesis of *S*-*tert*butyl acetothioacetate², treatment of ^tbutylthiol with sodium hydride, followed by quenching with diketene, gave a 57 % yield of the desired β -ketothioester, working at a 20-g scale; the yield was increased to 85 % at 1/4 scale. In an attempt to avoid the use of diketene in this preparation, and following previous studies on the use of 1,3-dioxin-4-ones as acetoacetylating reagents⁶, we have treated ^tbutyl thiol with 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (1), a reagent that has been successfully employed as a diketene equivalent ⁷ (Scheme I).

The actual acetoacetylating species in these reactions has been shown⁸ to be acetylketene (2), derived from thermal retro Diels-Alder decomposition of 1. For this reason, simultaneous removal of the other decomposition product, acetone, has

been considered necessary in order to avoid the formation of side products. This has been usually accomplished by carrying out the reaction in an open vessel and at a temperature of ca. 120 °C, which has prevented the use of 1 in the aceto-acetylation of volatile nucleophiles, such as ^tbutylthiol. However, we were able to show that the proposed reaction could be carried out under reflux conditions without significant formation of side products.

In our initial experiments, equimolecular amounts of the starting materials were refluxed for 12 h, affording the desired compound 3 in 78 % yield, together with dehydroacetic acid 4^9 (10 %), from [4+2] self-cycloaddition of acetylketene 2, and compound 5 (7 %), formed in the reaction between 4 and ^tbutylthiol. It was reasoned that partial evaporation of the thiol during the reflux might give rise to an excess of acetylketene and thus account for the formation of these side products. Therefore, the reaction was carried out using an excess of ^tbutylthiol, by means of periodic additions of this compound during the reflux. In these conditions, 3 was the only product, in an excellent 90 % isolated yield. The experimental procedure was much simpler than in the published method², and the reaction could be performed at a 20-g scale without any noticeable loss of yield.

In conclusion, 2,2,6-trimethyl-4H-1,3-dioxin-4-one provides an interesting alternative to diketene in the multigram-scale preparation of *S*-tert butylaceto-thioacetate, avoiding the use of an inert atmosphere and dry solvents and increasing the isolated yield to almost quantitative levels.

EXPERIMENTAL

2,2,6- Trimethyl -4H-1,3-dioxin-3-one (Aldrich) was distilled (70 °C, 1 torr) prior to use. The expression "petroleum ether" refers to the fraction with a boiling point of 40-60 °C. Bulb-to-bulb distillations were carried out using a Büchi GKR 51 kugelrohr apparatus; the reported temperatures are those at the oven. Melting points are uncorrected and were determined with a Büchi capillary apparatus. Combustion analyses were obtained with a Perkin Elmer 2400 CHN microanalyzer.

IR spectra were obtained with a Perkin Elmer 577 instrument. NMR spectra were recorded using a Varian VXR-300 spectrometer (300 MHz for 1 H, 75.4 MHz for 13 C).

<u>S-tertbutyl_acetothioacetate</u> (3). A solution of 2,2,6-trimethyl-4*H*-1,3dioxin-3-one 1 (20 g, 0.14 mol) in ^tbutylthiol (12.6 g, 0.14 mol) was refluxed for 12 h in an oil bath at 120 °C, with periodic additions of ^tbutylthiol (6 g) at 4-h intervals. The excess of ^tbutylthiol was distilled off under reduced pressure, and the residue was purified by kugelrohr distillation (90 °C, 0.7 torr, lit.², 95-100 °C, 0.9 nm) or by flash column chromatography, eluting with petroleum ether-ethyl ether (95:5), to afford 24.3 g (90 %) of pure **3**, as a pale orange oil. IR (film, NaCl): 1720, 1670 and 1615 cm⁻¹. ¹H-NMR (CDCl₃, 70 % *oxo* tautomer (**3a**), 30 % *enol* tautomer (**3b**)) δ ppm: 1.48 (s, 9H, ^tBu, **3a**), 1.51 (s, 9H, ^tBu, **3b**), 1.90 (s, 3H, C₄-H, **3b**), 2.26 (s, 3H, C₄-H, **3a**), 3.58 (s, 2H, C₂-H, **3a**), 5.35 (s, 1H, C₂-H, **3b**), 12.90 (s, 1H, OH, **3b**). ¹³C-NMR (CDCl₃) δ ppm: 20.84 (C₄, **3b**), 29.37 (C(CH₃)₃, **3a**), 29.94 and 29.95 (C(CH₃)₃, **3b** and C₄, **3a**), 47.87 (C(CH₃)₃, **3b**), 48.77 (C(CH₃)₃, **3a**), 58.95 (C₂, **3a**), 100.01 (C₂, **3b**), 172.76 (C₁, **3b**), 192.38 (C₁, **3a**), 195.87 (C₃, **3b**), 200.05 (C₃, **3a**).

When equimolecular amounts of the starting materials were used, column chromatography (silicagel, 95:5 petroleum ether-ethyl ether) of the crude reaction mixture afforded 78 % of 3, 10 % of dehydroacetic acid 4, and 7 % of 5.

<u>Data for 5</u>: Mp 72-74 °C (petroleum ether). Analysis: Calc. for $C_{12}H_{16}SO_3$: C, 60.00; H, 6.66. Found: C, 59.86; H, 6.90. IR: 1660, 1620 cm⁻¹. ¹H-NMR (CDCl₃) δ ppm : 1.55 (s, 9H, ^tBu), 2.24 (d, 3H, J=1.2 Hz, C₆-CH₃), 2.34 (s, 3H, COCH₃), 6.13 (d, 1H, J=1.2 Hz, C₅-H). ¹³C-NMR (CDCl₃): δ 18.08 and 19.45 (C₆-CH₃ and COCH₃), 29.49 (C(CH₃)₃), 49.20 (C(CH₃)₃), 114.29 (C₅), 126.88 (C₃), 164.10 and 164.83 (C₄ and C₆), 175.65 (C₂), 191.16 (COCH₃).

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- 9. Compound 4 is commercially available (Aldrich Chemical Company). Physical and spectral data were identical to those previously described.

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