Acta Chemica Scandinavica B 33 (1979) 460—468

Short Communications

Conjugate Addition of Lithium Dimethylcuprate to an α,β,β-Trialkylthio-α,β-unsaturated Ketone

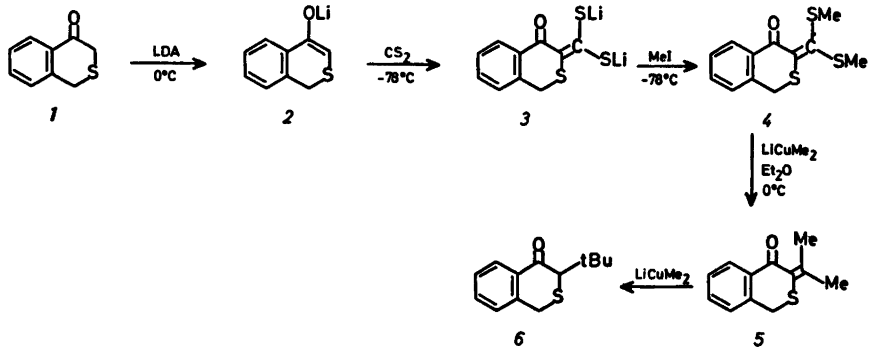
ØYVIND HAMMER JOHANSEN and KJELL UNDHEIM

Department of Chemistry, University of Oslo, Oslo 3, Norway

α-Alkylation of ketones is frequently complicated by side reactions.[1] In connection with studies of the 1*H*-2-benzothiopyran-4(3*H*)-one system,[2–4] we required the introduction of a 3-*t*-butyl group. Direct alkylation is not practical. Conjugate addition to α-*sec*-alkylidene ketones by an organometallic reagent, however, will furnish the *t*-alkyl derivative; similarly *sec*-alkyl derivatives will be available from *prim*-alkylidenes. Organocopper reagents are especially suitable for conjugate addition.[5] Introduction of an isopropylidene group into the 3-position of 1*H*-2-benzothiopyran-4(3*H*)-one by aldol condensation seemed unsatisfactory, since aldol condensation between methyl ketones and cyclohexanone largly occurs on the carbonyl group of the cyclohexanone and the methyl group of the other ketone.[6] The α-isopropylidene derivative of cyclohexanone can be made from 2-(dimethylthiomethylene)cyclohexanone and lithium dimethylcuprate;[7] further conjugate addition gives the *t*-butyl derivative. Similarly 2-(butylthiomethylene)cyclohexanone can be converted to 2-isopropylcyclohexanone.[8] It has also been reported that certain β-chloroenones are alkylated by lithium dimethylcuprate, *e.g.* 2-*t*-butylcyclohexanone is formed from 2-(1-chloroethylidene)cyclohexanone.[9] In the sulfur reactants an alkylthio group on the vinyl β-carbon is replaced by an alkyl group. In the corresponding thiopyran-4(3*H*)-one *4* there is an additional thio group on the α-carbon which might affect the course of the reaction. It is known, however, that alkenyl sulfides and most 2-alkylidedinethianes are inert to organocopper reagents,[10] and hence it seemed that breakage of the α-C—S bond with ring opening was unlikely.

The starting material for the synthesis was 1*H*-2-benzothiopyran-4(3*H*)-one[11] *1*, which was converted into its enolate *2* by lithium diisopropylamide (LDA). The enolate at −78 °C was reacted with carbon disulfide which results in dithiocarboxylation to *3*. The latter was *S*-methylated by means of methyl iodide to the α-dithiomethylene derivative *4*. Under these conditions one half of the enolate acts as a base since the α-proton after dithiocarboxylation is more acidic than the α-protons in *1* resulting in metal-hydrogen exchange between the initially formed dithiocarboxylated product and the enolate *2*. Addition of a second equivalent of LDA, however, led to a heterogeneous reaction. The use of a weaker base might have improved the yield.[7] The product *4* is identified by spectroscopic data; α,β-unsaturated *CO* in IR at 1640 cm^{-1}, *S*Me in ^1H NMR at δ 2.48, and the α,β-unsaturated *CO* in ^{13}C NMR at 131.5 (C-3), 149.4 (C=S_2), 182.8 (*CO*) and 19.0 ppm (*S*Me), and *M* (100 % rel. int.) at *m/e* 220.

The α-dimethylthiomethylene *4* was reacted with excess lithium dimethylcuprate without



Scheme 1.

0302-4369/79/060460-02$02.50

isolation of the intermediate isopropylidene *5* to yield the *t*-butyl derivative *6*. The product was isolated by chromatography. This experiment demonstrates the anticipated preferential breakage of the β-carbon–sulfur bond in α,β,β-trialkylthio-α,β-unsaturated ketones in reactions with lithium dimethylcuprate.

The spectroscopic data verify the structure of the product as *6*. In IR the *CO* stretch is seen at 1690 cm^{-1} and the mass spectrum has *M* at *m/e* 220 ($C_{13}H_{16}OS$). In ^1H NMR the *t*-butyl group is seen at δ 1.16 and the non-equivalent methylene protons (H-1) at δ 3.85 and 4.11. In ^{13}C NMR the *t*-butyl group is seen by the signals at 28.1 and 34.4 ppm; the spectrum is otherwise closely related to the spectrum published for *1*.[12]

Experimental. 3-Dimethylthiomethylene-1H-2-benzothiopyran-4-one 4. Freshly distilled THF (25 ml; $LiAlH_4$) and freshly distilled diisopropylamine (3.6 ml, 25 mmol; NaH) were mixed and 1.45 M [13] butyllithium (17.3 ml, 25 mmol) added at 0 °C by means of a syringe under purified and dry nitrogen. After stirring for 10 min at 0 °C a solution of 1*H*-2-benzothiopyran-4(3*H*)-one [11] (4.10 g, 25 mmol) in THF (50 ml) was added dropwise over 15 min. The mixture was stirred for 10 min at 0 °C, cooled to −78 °C and a solution of carbon disulfide (1.9 g, 25 mmol; dried over P_2O_5) in THF (10 ml) added slowly. The mixture was stirred for 20 min at −78 °C and slowly allowed to reach 0 °C before methyl iodide (7.1 g, 50 mmol) was added slowly. The reaction mixture was allowed to reach room temperature and left overnight before LiI was filtered off and the filtrate evaporated. The residue was extracted with chloroform, the chloroform solution washed, dried, and evaporated almost to dryness before thick layer chromatography on silica gel (Merck 60 PF_{254}; plates 20 cm × 40 cm and thickness 1.5 mm) using chloroform as developer. The yellow band with R_F 0.7–0.8 was scraped off, the substance extracted from the gel into chloroform and the chloroform solution evaporated; yield 68 % (34 %), m.p. 90–91 °C (light petroleum b.p. 80–100 °C). Anal. $C_{12}H_{12}OS_3$: C, H. ^1H NMR ($CDCl_3$): δ 2.48 (6H-$(SMe)_2$, s), 3.90 (2H-1, s), 7.1–7.5 (3H-arom), 7.9–8.1 (H-5, m). ^{13}C NMR ($CDCl_3$): δ 19.0 (S-Me, q), 31.2 (C-1, t), 126.4, 127.8, 128.8, and 132.1 (C-5–C-8, d) 131.5 (C-2, s), 135.3 (C-4a, s), 139.0 (C-8a, s), 149.4 (=C=S_2), 182.8 (CO, s). IR (CCl_4): 1640 cm^{-1} (α,β-unsat. CO). UV [$CHCl_3$, (log ε)]: 285 (3.90), 420 (3.89) nm. MS [70 eV, *m/e* (% rel. int.)]: 268 (100 %, M), 253 (31), 221 (17), 207 (6), 177 (7), 175 (17), 118 (54), 103 (67).

3-t-Butyl-1H-2-benzothiopyran-4(3H)-one 5. Copper iodide (9.6 g, 50 mmol) in a Soxleth extraction apparatus was purified by heating with anhydrous THF for 12 h and dried *in vacuo* at room temperature.[14] The copper iodide in ethyl ether (180 ml, $LiAlH_4$) was cooled to 0 °C and 1.6 M methyllithium [15] (63 ml, 100 mmol) added under dry and purified nitrogen. The resultant mixture was stirred for 10 min before a solution of 3-dimethylthiomethylen-1*H*-2-benzothiopyran-4-one (1.75 g, 6.5 mmol) in anhydrous ether (175 ml) was added dropwise. The reaction mixture was stirred for 5 h at 0 °C and then poured into 1.2 M HCl (1000 ml) with stirring. The ether phase was collected, the aqueous phase extracted with ether and the combined and dried ($MgSO_4$) ether solutions evaporated. The residual material was chromatographed on thick layer silica gel as above using chloroform. The band with R_F 0.6–0.7 was scraped off and the substance extracted from the gel into chloroform. The residue after evaporation of the chloroform was subjected to preparative GLC on 10 % Apiezon L (d. 6 mm, l. 240 cm; gas flow 60 ml/min) at 240 °C; retention time 5 min. The yield was 20 % of an oily material which solidified below 10 °C. MS: M *m/e* 220.0917; calc. for $C_{13}H_{16}OS$: 220.0922. ^1H NMR ($CDCl_3$): δ 1.16 (9H *t*-Bu, s), 3.36 (H-3, s), 3.85 and 4.11 (2H-1, AB, *J* 17 Hz), 7.0–7.5 (3H-arom), 7.8–8.0 (H-5, m). IR (film): 1690 cm^{-1} (CO). ^{13}C NMR ($CDCl_3$): δ 28.1 (Me in *t*-Bu, q), 30.5 (C-1, t), 34.4 (C in *t*-Bu, s), 57.9 (C-3, d), 127.2, 127.5, 128.7 and 132.0 (C-5–C-8), 135.1 (C-4a, s), 140.5 (C-8a, s) and 192.7 (C-4, s). MS [70 eV, *m/e* (% rel. int.)]: 220 (1, M), 219 (3), 205 (2), 166 (3), 164 (*100*), 163 (18), 131 (13), 118 (47).

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Received May 2, 1979.