Notes

Nucleophilic Additions to Diethyl Cyclopropylmethylidenemalonate

Samuel Danishefsky* and George Rovnyak

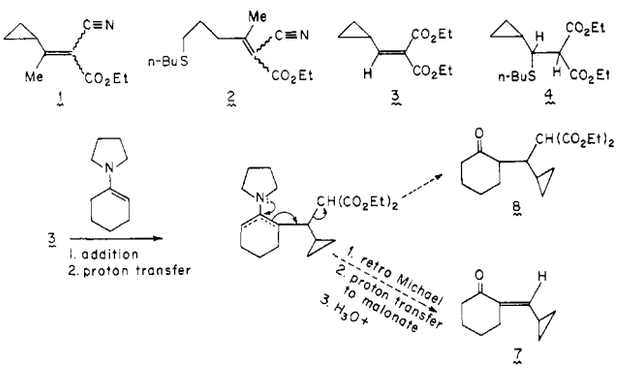
Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260

Received April 22, 1974

The reaction of *n*-butyl mercaptan with ethyl α-cyano-β-cyclopropylcrotonate (**1** cis and trans mixture) has been reported to give ethyl 2-cyano-3-methyl-6-*n*-butylmercaptohex-2-enoate (**2**, cis and trans mixture).[1] In the light of the greater receptivity of α,β-unsaturated carbonyl systems toward 1,4-addition relative to equivalently activated cyclopropanes,[2] it appeared that the generality of this type of terminal attack merited further examination. The particular substrate which we chose for study was the cyclopropylmethylidenemalonate, **3**. This compound was easily prepared (78%) by the Knoevenagel condensation of cyclopropanecarboxaldehyde[3] with diethyl malonate under the influence of ammonium acetate.

The condensation of **3** with *n*-butyl mercaptan was studied under neutral as well as base-catalyzed conditions. In both cases the only product obtained (71 and 75% yields, respectively) was the simple 1,4 adduct, **4**. We could find no evidence for the presence of ring-opened products similar to those obtained in the case of **1**. Apparently, in the latter case, the β,β disubstitution hinders simple Michael addition. Whether the ring-opened product, **2**, results from *bona fide* nucleophilic attack in a "homo" extended conjugate sense or is the result of a free-radical pathway[4] is not known. Such a free-radical mechanism has been implicated[5] in the ring-opened products arising from the reaction of 1,1-dicarbethoxy-2-vinylcyclopropane (**5**) with *n*-butyl mercaptan.

Since the thermal reaction of **5** with enamines occurs *via* overall terminal attack,[6,7] it was of interest to investigate the corresponding reaction for the case of **3**. Accordingly, compound **3** was heated in toluene with a twofold excess of 1-*N*-pyrrolodinocyclohexene (**6**). After acidic hydrolysis, the reaction residue was separated by fractional distillation. The products obtained in ascending order of boiling points were (1) a mixture of cyclohexanone and diethyl malonate, the latter in *ca.* 40% yield; (2) 2-cyclopropylmethylidenecyclohexanone (**7**) in 40–45% yield; and (3) 2-carbethoxy-3-cyclopropyl-3-(cyclohexan-2-on-1-yl) propionate (**8**) in 15% yield. An attractive sequence which accounts for these results is set forth below. The key step leading to **7** is formulated as a reverse Michael reaction, with malonate as the leaving group, coupled at some stage to a proton transfer. It will be seen that this scheme invokes the tetrasubstituted enamine isomer on the pathway to the major product. In the case of pyrrolidine enamines, the trisubstituted isomer is expected to predominate.[8] However, under the vigorous reaction conditions, equilibration between the tri- and tetrasubstituted tautomers could well be anticipated.



The generality of synthesizing α-alkylidenecycloalkanones *via* a Michael–retro-Michael combination between the corresponding enamines and alkylidenemalonates remains to be explored. In the case at hand, the trans configuration is tentatively assigned to compound **7** on the basis of the 2 Hz allylic coupling constant of its vinylic proton.

Recently, Grieco[9] reported exclusive 1,4-addition of lithium dimethylcopper to **3**. It would thus appear to be safe to generalize that, for the case of this substrate, extension of conjugation by the cyclopropane ring is not manifested at the chemical level.[10]

Experimental Section[11]

Preparation of Cyclopropylmethylidenemalonate (3). A solution of 9.96 g (0.056 mol) of diethyl malonate, 5.0 g (0.071 mol) of cyclopropanecarboxaldehyde,[3] 0.727 g (0.012 mol) of acetic acid, and 0.463 g (0.006 mol) of ammonium acetate in 10 ml of dry benzene was heated under reflux, with the condensate collected in a Dean-Stark trap. After 4 hr, 1.1 ml of water was collected.

The solution was poured into ether and extracted with water. After being dried, the organic fraction was concentrated *in vacuo*. The residue was distilled to give **3**: 9.3 g (0.044 mol, 78%); bp 74–75° (0.025 mm); λ_{max} (CCl_4) 320, 5.80, 6.11 μ; nmr (CCl_4) τ 3.70 (d, J = 11 Hz, 1 H), 5.76 (q, J = 7 Hz, 2 H), 5.84 (q, J = 7 Hz, 2 H), 7.8–8.4 (m, 1 H), and 8.5 ppm (m, 10 H, containing t at 8.77, J = 7 Hz); *m/e* 212 (parent), 110 (base).

Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60%. Found: C, 62.15; H, 7.65%.

Reactions of 3 with *n*-Butyl Mercaptan. Formation of Mercapto Diester 4. Method A. To a 100-ml glass pressure flask was added 3.0 g (0.0141 mol) of **3** and 7.08 g (0.078 mol) of *n*-butyl mercaptan. The solution was purged with nitrogen, sealed, and heated at 110° for 48 hr. Excess mercaptan was removed under reduced pressure and the residue was distilled *in vacuo* to give 0.05 g (16%) of recovered **3** as forerun and 3.03 g (71%) of diester sulfide **4**, bp 110 ° (0.1 mm).

Method B. To a suspension of 41 mg (1.7 mmol) of sodium hydride in 10 ml of dry dimethoxyethane was added 1.53 g (17 mmol) of *n*-butyl mercaptan and 3.0 g (14.1 mmol) of **3**. The solution was heated under reflux for 4 hr. The solution was concentrated *in vacuo*, diluted with ether, and extracted with water. The organic layer was dried ($CaCl_2$) and then concentrated at reduced pressure. Vacuum distillation of the residue afforded, after removal of a forefraction, 3.2 g (75%) of **4**: bp 116–118° (0.2 mm); λ_{max} (CCl_4) 3.21, 5.70 sh, 5.77, 9.58, 9.79, and 10.48 μ; nmr τ 5.88 (q, J = 7 Hz, 4 H), 6.45 (d, J = 9 Hz, 1 H), 7.15–7.60 (m, 3 H), 8.2–9.8 ppm (m, 18 H containing t, J = Hz, at 8.78 ppm); *m/e* 302 (parent), 67 (base peak).

Anal. Calcd for $C_{15}H_{26}O_4S$: C, 59.60; H, 8.60; S, 10.60. Found: C, 59.44; H, 8.46; S, 10.39.

Reaction of 3 with 1-Pyrrolodinocyclohexene.[9] Formation of 7 and 8. A solution of 3.5 g (23.2 mol) of the enamine[8] and 2.5 g (11.8 mmol) of **4** in 10 ml of toluene was heated under reflux for 5 days. The solution was diluted with ether and extracted with 3 ml of dilute HCl. The ether fraction was dried ($CaCl_2$) and concentrated *in vacuo* and the residue was submitted to fractional distillation. A fraction distilling at 100–110° (25 mm) was shown by nmr integration to consist of *ca.* 3:2 diethyl malonate (41% yield):cyclohexanone. A second fraction (1.15 g) distilling at 68–70° (0.025 mm), was chiefly (*ca.* 85% pure) **7** (41% yield). The highest boiling

fraction [118–120° (0.025 mm)] was chiefly (85% pure) **8** (15% yield). Further purification of **7** and **8** was effected by distillation at 55 (0.005 mm) and 116° (0.005 mm), respectively.

For **7**: λ_{max} (CCl_4) 3.19, 3.29, 5.83, 5.93, and 6.12 μ; nmr (CCl_4) τ 4.24 (d, J = 10.5 Hz, of t, J = 2 Hz, 1 H), 7.25–9.3 ppm (m, 13 H); *m/e* 150 (parent), 122 (base peak).

For **8**: λ_{max} (CCl_4) 5.70 sh, 5.7, 9.41 sh, 9.67 μ; nmr (CCl_4) τ 5.88 (q, J = 7 Hz, 4 H), 6.3 (d, J = 7 Hz, 1 H), 6.8 (m, 1 H), 7.1–9.9 ppm (m, 20 H, containing t, J = 7 Hz, at 8.77 ppm); *m/e* 310 (parent), 264 (base peak).

Acknowledgments. This research was supported by PHS Grant CA 12107-07. NDEA and Andrew Mellon Fellowships for G. R. are gratefully acknowledged.

Registry No.—**3**, 39000-53-8; **4**, 51933-04-1; **7**, 51933-05-2; **8**, 51933-06-3; diethyl malonate, 105-53-3; cyclopropanecarboxaldehydes, 1489-69-6; *n*-butyl mercaptan, 109-79-5; 1-pyrrolidinocyclohexene, 1125-99-1.

References and Notes

(1) J. M. Stewart and D. R. Olsen, *J. Org. Chem.*, **33**, 4534 (1968).
(2) For instance, monoactivated cyclopropanes such as ethyl cyclopropanecarboxylate do not react with enamines up to 175° whereas acrylates react at room temperature. Similarly, diethyl cyclopropane-1,1-dicarboxylate is considerably less reactive toward amines, enamines, and thiols relative to diethyl methylenemalonate.
(3) H. C. Brown and H. Tsukamoto, *J. Amer. Chem. Soc.*, **83**, 2016 (1961).
(4) It is interesting to note that mercaptan was the only nucleophile which gave terminal addition with **1**.
(5) S. Danishefsky and G. Rovnyak, *J. Chem. Soc., Chem. Commun.*, 820 (1972).
(6) S. Danishefsky, G. Rovnyak, and R. Cavanaugh, *J. Chem. Soc., Chem. Commun.*, 636 (1972).
(7) See S. Danishefsky and G. Rovnyak, *Chem. Commun.*, 822 (1969), for a mechanistic account of this reaction.
(8) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Amer. Chem. Soc.*, **85**, 207 (1963).
(9) P. A. Grieco and R. Finkelhor, *J. Org. Chem.*, **38**, 2100 (1973).
(10) T. A. Wittstruck and E. N. Trachtenberg, *J. Amer. Chem. Soc.*, **89**, 3810 (1967).
(11) Boiling points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 137 Infracord spectrophotometer. Nmr spectra were measured on a Varian Associates A-60 spectrometer. Combustion analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

Preparation and Reactions of a Tris Annelating Agent

Samuel Danishefsky* and Paul Cain

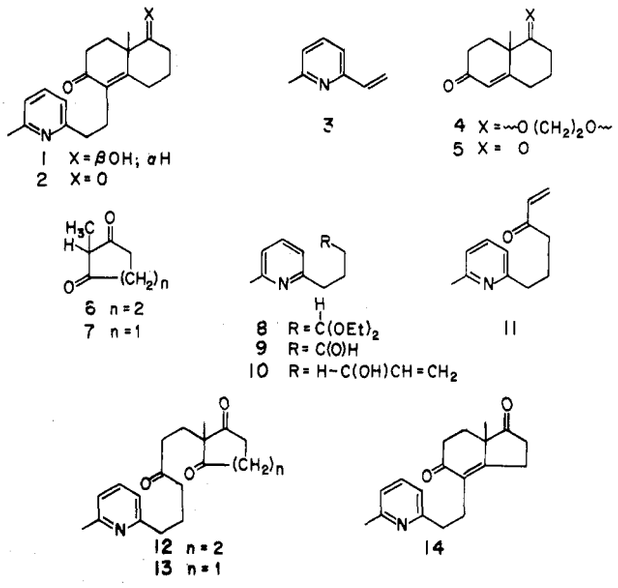
Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260

Received April 22, 1974

Recently we reported the synthesis of *dl*-D-homoestrone *via* the picolylethylated octalone derivative **1**.[1] This intermediate was assembled by the Michael reaction of ketalenone **4** with bis annelating agent[2] **3**. Precursor **4** is the monoketalization product[3,4] of the Wieland–Miescher ketone **5**, itself the Robinson annelation product of diketone **6** with methyl vinyl ketone.[5,6] The vinylpicoline **3**[7] is obtained in low yield[7] *via* hydroxymethylation of 2,6-lutidine.

A major simplification in the lutidine route to 19-norsteroids could be contemplated by the utilization of the tris annelating agent **11**. Were this compound to be easily available, its merger with diketones (*e.g.*, **6**) to produce, directly, products such as **2** could be envisioned as a means of eliminating the lowest yield facets of the synthetic approach described above. Below we set forth a convenient and efficient synthesis of **11**. Its high-yield condensations with **6** and **7** are also described.

Treatment of 2,6-lutidine with phenyllithium followed by alkylation of the resultant anion with 3-chloropropionaldehyde diethyl acetal[8] gives **8**, which is converted, without purification, to aldehyde **9** (70% overall). Addition of



vinylmagnesium chloride to **9** gives (89%) alcohol **10** which undergoes oxidation by manganese dioxide to afford (88%) the desired **11**.

Some indication of the potential applications of this compound can be seen from the following experiments. Under the influence of sodium hydride, enone **11** couples smoothly with **6** to give **12**. Cyclization of **12** under the influence of 3-aminopropionic acid[9] affords (75%) **2**, which is converted to its crystalline dihydro derivative **1**.

Condensation of **7** with **11** can be conducted in one step in aqueous acid to give enedione **14** in 92% yield. Alternatively **7** and **11** can be coupled through the action of triethylamine in ethyl acetate[10] to give trione **13**, which can be cyclized, in a separate step, *via* 3-aminopropionic acid[9] to give **14**.

The advantages[9] of passing through symmetrical intermediates such as **12** and **13** on the way to compounds such as **2** and **14** will be set forth in future publications.

Experimental Section[11]

Preparation of Picolylbutyraldehyde 9. To a stirred solution containing 16.2 g (0.15 mol) of 2,6-lutidine in 250 ml of dry THF (freshly distilled from CaH_2) under a nitrogen atmosphere was slowly added 65 ml (0.15 mol) of 2.4 *M* PhLi in 70:30 benzene–ether. The resulting solution was stirred at room temperature for 20 min. After cooling to 0°, 10.6 g (0.10 mol) of 3-chloropropionaldehyde diethyl acetal was slowly added. After stirring for 30 min at 0°, the solution was refluxed for 12 hr. The solution was then cooled to room temperature, 150 ml of aqueous 10% HCl was slowly added, and the resulting solution was stirred for 5 hr. The solution was then neutralized with $NaHCO_3$ and extracted with 5 × 100 ml CH_2Cl_2, and the combined organic extracts were dried over anhydrous Na_2SO_4. After evaporation of the solvents, distillation afforded 10.84 g (70%) of **9** as an oil: bp 64–65° (0.05 mm); ir ($CHCl_3$) 2810, 2710, 1715, 1590, 1575 cm^{-1}; nmr (CCl_4) δ 1.8–2.4 (m, 4 H), 2.48 (s, 3 H), 2.68 (t, 2 H), 6.90 (d, 2 H), 7.38 (t, 1 H); *m/e* 163.

Although this material was judged to be pure by nmr, two combustion analyses[11] gave results not in accord with prediction.

Preparation of Allylic Alcohol 10. To a stirred solution containing 8.2 g (0.05 mol) of aldehyde **9** in 150 ml of dry THF (freshly distilled from CaH_2) under a nitrogen atmosphere and at −78° was slowly added 26.4 ml (0.075 mol) of 2.84 *M* vinylmagnesium chloride in THF. The resulting solution was stirred for 0.5 hr at −78° and then at room temperature for 1.5 hr. The solution was then poured into 50 ml of H_2O and acidified with 10% HCl. After neutralization with $NaHCO_3$, the organic layer was separated and the aqueous layer was extracted with 4 × 50 ml of CH_2Cl_2. Evaporation of the solvent and filtration of the residue through 150 g of silica gel using 3:1 hexane–ethyl acetate as the eluent afforded 8.5 g (89%) of the desired allylic alcohol **10** as a pale yellow oil: ir