Pyrolytic Aromatization of Dimethyl 3,5,6,7,8,8a-Hexahydro-5,5,8a-trimethyl-1,2-naphthalenedicarboxylate

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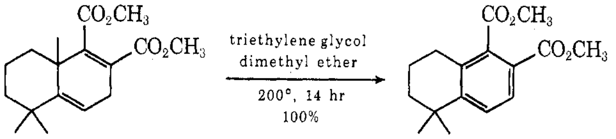
Pyrolytic aromatization reactions involving the elimination of a bridgehead methyl group are seldom of synthetic utility. Thus, the pyrolysis of steroidal 10-methyl ring A dienones to 19-norphenolic steroids are characterized by reaction temperatures between 300 and 700° and yields of less than 30%.[2] Similarly, pyrolytic aromatizations of bis-$\Delta^{5,8(9)}$-steroidal dienes to the corresponding ring B aromatic steroids are usually effected in low yields.[3-10]

We wish to report a high-yield pyrolytic aromatization involving the elimination of a bridgehead methyl group under exceptionally mild conditions. Previously unreported dimethyl 3,5,6,7,8,8a-hexahydro-5,5,8a-trimethyl-1,2-naphthalenedicarboxylate (**1**), prepared in 69% yield by the Diels-Alder reaction of 1-vinyl-2,6,6-trimethylcyclohexene with dimethyl acetylenedicarboxylate, is quantitatively aromatized to dimethyl 5,6,7,8-tetrahydro-5,5-dimethyl-1,2-naphthalenedicarboxylate (**2**) by heating in triethylene glycol dimethyl ether at 200° for 14 hr. At *m/e* greater than 178 (M^+ of solvent) the mass spectra of the reaction mixture and an analytical sample of **2** were identical. The nmr spectrum of the isolated product exhibited peaks due to a trace of residual solvent but was otherwise identical with the spectrum of the analytical sample. To the extent that the results of pyrolytic aromatization studies of various methyl-substituted 1,4-cyclohexadienes[11-14] apply to the aromatization of **1**, the reaction probably goes through a nonchain radical process.



1 **2**

Whereas **1** is a useful intermediate for the synthesis of many sesquiterpenes, **2** should prove to be useful for the synthesis of compounds such as the tanshinones[15] or 4,4-dimethyl ring B aromatic steroids.

Experimental Section

Dimethyl 3,5,6,7,8,8a-Hexahydro-5,5,8a-trimethyl-1,2-naphthalenedicarboxylate (**1**).—A mixture of 12.92 g (0.086 mol) of 1-vinyl-2,6,6-trimethylcyclohexene and 25 ml of dimethyl acetylenedicarboxylate was mechanically stirred and heated on a steam bath under nitrogen for 71 hr. Prolonged heating at higher temperatures causes the dimethyl acetylenedicarboxylate to tetramerize.[16] Vacuum distillation gave 17.35 g (69%) of **1** contaminated with a small amount of **2**: bp 135° (0.13 mm); uv max (MeOH) end absorption; ir (neat) 1725 (C═O), 1670, 1630 (C═C), 1250 cm^{-1} (CO); nmr (CCl_4) δ 5.92–5.49 (dd, 1, J = 3.0, 2.6, 3.0 Hz, ═CH), 3.70 (s, 6, OCH_3), 3.00 (d, 1, J = 5.6 Hz, ═$CHCH_2$), 2.8 (d, 1, J = 3.0 Hz, ═$CHCH_2$), 1.70–1.27 [m, 6, $(CH_2)_3$], 1.37 (s, 3, bridgehead CH_3), 1.17 (s, 3, geminal CH_3), 1.13 (s, 3, geminal CH_3); mass spectrum (70 eV) *m/e* (rel intensity), 292 (2), 277 (13), 260 (26), 245 (100), 233 (37), 213 (98), 163 (37).

Anal. Calcd for $C_{17}H_{24}O_4$: C, 69.84; H, 8.27. Found: C, 70.03; H, 8.51.

Dimethyl 5,6,7,8-Tetrahydro-5,5-dimethyl-1,2-naphthalenedicarboxylate (**2**).—A solution of **1** (0.5 g) in 5 ml of triethylene glycol dimethyl ether was heated at 200° for 14 hr. The reaction mixture was diluted with chloroform and extracted with water. Concentration of the dried (sodium sulfate) chloroform solution gave a quantitative yield of **2**, as a pale yellow oil: uv max (pentane) 241 nm (ϵ 9400), 281 (1500), 289 (1450); ir (neat) 1725, 1735 (C═O), 1590 (aromatic CH), 1275, 1290 cm^{-1} (CO); nmr (CCl_4) δ 7.38 and 7.75 (ABq, 2, J = 9 Hz, aromatic H), 3.85 (s, 6, OCH_3), 2.86–2.54 (m, 2, benzyl CH_2), 2.13–1.50 [m, 4, $(CH_2)_2$], 1.33 [s, 6, $(CH_3)_2$]; mass spectrum (70 eV) *m/e* (rel intensity) 276 (4), 261 (9), 245 (37), 244 (100), 229 (49), 213 (4), 201 (8), 186 (21), 142 (8).

Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.55; H, 7.30. Found: C, 70.00; H, 7.47.

Registry No.—**1**, 36963-51-6; **2**, 36963-52-7.

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The Enamine as a Cyclohexylidene Source

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The recent observation of Alt and Gallegos[1] that enamines react with cyanoacetic acid to produce alkylidenecyanoacetic acids has led us to examine the limitations of 1-morpholino-1-cyclohexene as an intermediate for the preparation of cyclohexylidene derivatives (Knoevenagel products).

Malonic acid derivatives which contain at least one cyano group (cyanoacetic acid derivatives) react with the enamine in an exothermic reaction within 30 min, producing the expected product in at least 59% yield. On the other hand, several other compounds having active methylene groups (phenylacetonitrile, ethyl malonate, acetylacetone, chloroacetic acid, and chloroacetonitrile) failed to give a condensation product even with extensive boiling. The limitation is essentially the same as documented so carefully by Hein, Astle, and

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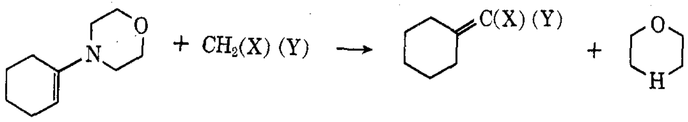
[1] G. H. Alt and G. A. Gallegos, *J. Org. Chem.*, **36**, 1000 (1971).

Table I

Reaction of 1-Morpholino-1-cyclohexene with Active Methylene Compounds



Registry no.	No.	Methylene X	Methylene Y	Reacting conditions Solvent	Reacting conditions Temp, °C	Reacting conditions Time	Mp or bp, °C (mm)	Yield, %	Registry no.	Ir,[a] cm⁻¹ CN	Ir,[a] cm⁻¹ C=O	Ir,[a] cm⁻¹ C=C	Nmr,[b] δ, CH₂ (cis)
372-09-8	**1**	CN	COOH	DMF	25–30	30 min	110–112[c]	81.4	37107-50-9	2230	1705	1590	2.72 (CN) 3.01 (COOH)
105-56-6	**2**	CN	$COOC_2H_5$	None	25–30	20 hr	152–157 (10)[d]	59.1	6802-76-2	2225	1725	1595	2.63 (CN) 2.93 ($COOC_2H_5$)
109-77-3	**3**	CN	CN	DMF[e]	25–30	30 min	138–146 (10–8)[f]	58.7	4354-73-8	2245		1595	2.55 (CN)
107-91-5	**4**	CN	$CONH_2$	Abs EtOH[g]	Reflux	10 min	105–110[g]	76.1	704-16-5	2215	1670	1585	2.62 (CN) 2.92 ($CONH_2$)
141-82-2	**5**	COOH	COOH	DMF	25–30	7 days	135–140	19.6[h]	4354-70-5		1690	1620	2.80 (COOH)
	6	COOH	COOH	DMF	58–65	15 hr	70–83[i]	60.0	1552-91-6		1695	1645	2.23 (H) 2.82 (COOH)
1071-46-1	**7**	COOH	$COOC_2H_5$	DMF	55–70	8 hr	99–103 (8)	28.7[j]	1552-92-7		1715	1650	2.17 (H) 2.84 ($COOC_2H_5$)

[a] Infrared spectra were determined in chloroform (**1**, **4**), neat (**2**, **3**, **7**), in carbon tetrachloride (**6**), and as a Nujol mull (**5**). [b] Nmr response of methylenes cis to the substituent in chloroform (**1**, **4**), neat (**3**, **7**), carbon tetrachloride (**2**, **6**), and pyridine (**5**). [c] Reported mp 110–110.5°: A. C. Cope, *et al.*, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 234. [d] Reported bp 98–99° (0.1 mm), ref 2. Nmr taken by T. Izewski. [e] An equivalent of acetic acid was required to buffer the mixture. Omission of the acetic acid resulted in an 83% yield of dimer, mp 107–140°. After recrystallization the melting point was 171–175°, as reported by M. R. S. Weir and J. B. Hyne, *Can. J. Chem.*, **42**, 1440 (1964). [f] Reported bp 98–101° (0.08 mm), ref 2. [g] An equivalent of acetic acid was required to buffer the mixture, avoiding complex products formed in base [*cf.* F. B. Thole and J. F. Thorpe, *J. Chem. Soc.*, **99**, 422 (1911)]. Product crystallized directly from reaction mixture. The reported melting point is 110.5–111.5°, ref 2. [h] A 25% excess of malonic acid was used and the dibasic acid was accompanied by an 18.9% yield of monobasic acid. Crystallization from ethyl acetate–hexane furnished purified product, mp 146–147.5°, reported mp 150° [G. A. R. Kon and E. A. Speight, *J. Chem. Soc.*, 2727 (1926)]. [i] The monbasic acid, cyclohexylideneacetic acid, was the product when the malonic acid to enamine ratio was 2:1. Crystallization from alcohol–water results in mp 90–92°, as reported by Papa and Schwenck (ref 4). [j] Ethyl hydrogen malonate was generated *in situ* by action of the potassium salt and chloroacetic acid. Ethyl cyclohexylideneacetate was the product. The reported boiling point is 88–90° (10 mm) [W. S. Wadsworth and W. D. Emmons, *J. Amer. Chem. Soc.*, **83**, 1733 (1961)].

Shelton[2] in their ion-exchange resin catalysis study of the Knoevenagel condensation.

We have, however, observed a reaction with malonic acid. If 1-morpholino-1-cyclohexene was allowed to stand with malonic acid for 7 days at room temperature a mixture of cyclohexylidenemalonic acid (20% yield) and cyclohexylideneacetic acid (19%) was obtained. By heating a 2:1 ratio of malonic acid and the enamine at 60–65° for 15 hr a good yield (60%) of cyclohexylideneacetic acid was produced. This procedure is much more effective than the direct Knoevenagel procedure said to give less than 5% yield.[3] Furthermore, the procedure is much more convenient than the Reformatsky reaction usually used.[4]

Ethyl hydrogen malonate[5] has also proved to be effective in producing ethyl cyclohexylideneacetate (29%). Here the potassium salt was more convenient and the product was apparently free of the endo isomer, ethyl 1-cyclohexenylacetate, based on nmr.

Experimental Section

All melting points and boiling points were uncorrected. A Varian A-60 nmr spectrophotometer was used for recording nmr spectra in parts per million (δ) with respect to tetramethylsilane. A Beckman IR-8 or Perkin-Elmer 337 was used to record infrared spectra.

Reaction of 1-Morpholino-1-cyclohexene with Active Methylene Compounds.—The enamine was added to an equimolar amount of active methylene compound ($CH_2(X)(Y)$) in dimethylformamide (250 ml/mol). After the exothermic reaction was over (or heating concluded), the product was treated with dilute hydrochloric acid and the reaction was worked up by extraction with ether. Acidic products were washed out with 10% sodium carbonate, precipitated with hydrochloric acid, and collected. Liquid, neutral products were distilled at reduced pressure. The results are assembled in Table I.

Registry No.—1-Morpholino-1-cyclohexene, 670-80-4.

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^1H Nuclear Magnetic Resonance Structure Elucidation of Substituted Isoquinolines by Means of $Eu(fod)_3$[1a]-Induced Paramagnetic Shifts

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Research efforts in this laboratory have led to the synthesis of a number of substituted isoquinolines. The determination of the position of substitution in these and other heterocyclic systems is by no means a trivial task, and in many instances classical and spectroscopic determinations lead to equivocal results.

The recently developed lanthanide-induced shift reagents[2] have found extensive application in structure elucidation, and we report here the application of

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(1) (a) $Eu(fod)_3$, tris(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyloctane)-4,6-dionatoeuropium(III): R. E. Rondeau and R. E. Sievers, *J. Amer. Chem. Soc.*, **93**, 1522 (1971). (b) National Research Council Postdoctoral Research Associate, 1971–1972.

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