Table I
Spectral Data of *cis*- and *trans*-Methyl α-(Tetrahydro-2-furylidene)acetate

	cis-	*trans*-
Ir, λ_{max} (film)	1702, 1644 cm^{-1}	1701, 1641 cm^{-1}
Pmr, δ_{TMS} (CCl_4)	C-3 H's (2.64, m)	C-3 H's (3.03, m)
	C-4 H's (2.00, m)	C-4 H's (2.02, m)
	C-5 H's (4.30, t, J = 6.5 Hz)	C-5 H's (4.13, t, J = 7 Hz)
	C-6 H (4.64, t, J = 1.2 Hz)	C-6 H (5.11, t, J = 1.5 Hz)
	C-8 H's (3.53, s)	C-8 H's (3.54, s)
Cmr, ppm (TMS, $CDCl_3$)	C-2 (172.26)	C-2 (176.99)
	C-3 (32.18)	C-3 (30.33)
	C-4 (23.28)	C-4 (23.92)
	C-5 (74.42)	C-5 (71.90)
	C-6 (87.79)	C-6 (89.12)
	C-7 (166.41)	C-7 (168.88)
	C-8 (50.62)	C-8 (50.52)

with sodium hydride in THF or sodium methoxide in methanol resulted in the formation of a mixture of cis and trans isomers in ratios of 23:77 and 21:79, respectively. We note also that treatment of the trifluoroacetoxy compound **3** with thallous ethoxide in ethyl ether gave a similar mixture of cis and trans isomers in a ratio of 28:72.

Stereochemical assignments are based on (a) ir, pmr, and cmr data (see Table I), (b) the observed ease of conversion of the cis isomer into the trans isomer, and (c) nmr shift reagent studies using tris(dipivalomethanato)europium(III) or Eu(DPM)$_3$.[1] With Eu(DPM)$_3$ larger deshielding effects were observed for the C-3 hydrogens in the trans isomer **1**, where these allylic hydrogens are close to the carbonyl group, than in the cis isomer **2**, where the corresponding methylene hydrogens are well removed from the carbonyl group.

Experimental Section

Preparation of *trans*-Methyl 3-Iodo-6-hydroxy-2-hexenoate. To a solution of *trans*-methyl 3-iodo-6-trifluoroacetoxy-2-hexenoate (3.66 g, 10 mmol) in 2.5 ml of methanol and 5 ml of tetrahydrofuran was added a solution of potassium carbonate (1.38 g, 10 mmol) in 25 ml of water. The resulting mixture was stirred for 4 hr at room temperature and then extracted with ethyl ether (3 × 25 ml). The combined ether extracts were washed with water (25 ml) and saturated sodium chloride solution and dried (Na_2SO_4). The solvent was removed *in vacuo* to give 2.56 g of a pale yellow oil which was distilled (Kugelrohr oven, 150°, 0.9 mm) to yield 2.48 g (92%) of *trans*-methyl 3-iodo-6-hydroxy-2-hexenoate: λ_{max} (film) 3400, 1720, 1620, 1180 cm^{-1}; pmr δ_{TMS} (CCl_4) 6.37, (s, 1, C-2 H), 3.62 (m, 6, C-6, C-7 H's, OH), 2.80 (m, 2, C-4 H's), 1.78 (m, 2, C-3 H's).

Preparation of *cis*-Methyl α-(Tetrahydro-2-furylidene)acetate. To a suspension of silver oxide (0.765 g, 3.3 mmol) in ethyl ether (10 ml, distilled from sodium) was added *trans*-methyl 3-iodo-6-hydroxy-2-hexenoate (0.81 g, 3 mmol). The mixture was stirred under nitrogen at room temperature overnight and then filtered through a pad of Celite to remove the silver salts. The solvent was removed *in vacuo* to give 0.60 g of a light yellow oil which was a 1:1 mixture of starting material and desired product (determined by nmr). The oil was partially distilled[6] (Kugelrohr oven, 107°, 0.6 mm) and then partially redistilled (Kugelrohr oven, 107° 0.6 mm) to afford a sample of *cis*-methyl α-(tetrahydro-2-furylidene)acetate pure enough for spectral analysis: mass spectrum *m/e* 142 (see Table I for other spectral data).

Acknowledgment. We gratefully acknowledge the support of the American Cancer Society (Grant IC-83).

Registry No.—**1**, 52196-15-3; **2**, 52196-16-4; **3**, 51755-87-4; **4**, 52259-83-3.

References and Notes

(1) T. A. Bryson, *J. Org. Chem.*, **38**, 3428 (1973); see also footnote 5.
(2) F. F. Blick and B. A. Brown, *J. Org. Chem.*, **26**, 3685 (1961).
(3) T. A. Bryson, *Tetrahedron Lett.*, 4923 (1973).
(4) All compounds were analyzed by ir and nmr before and after each distillation.
(5) Similar *trans*-furylidene acetates have been prepared: S. J. Danishefsky, *et al.*, private communication.
(6) Since the starting alcohol has a boiling point slightly higher than that of the desired product, partial distillation increased the percentage of lower boiling component in the mixture (**2**, estimated to be better than 85% pure by pmr).

Dissolving Metal Reductions of Benzylic Esters[1a]

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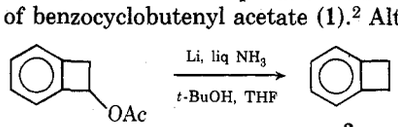
Recently we reported a convenient route to benzocyclobutene (**2**) in which the novel step was the dissolving metal reduction of benzocyclobutenyl acetate (**1**).[2] Although this



1 2

reductive cleavage was patterned after a similar reaction of allylic acetates,[3] the above reaction was to our knowledge its first application to a benzylic system. The benzyl moiety is frequently employed as a protecting or activating group because its subsequent removal can be effected by hydrogenolysis[4] or hydrostannolysis.[5] The latter procedure, however, failed to bring about the conversion of **1** to **2**.[2] In view of such a difference, it seemed desirable to define the scope of this dissolving metal reductive cleavage. In order to investigate the effect of the ester group six benzylic compounds were selected: acetate (**3**), benzoate (**4**), carbamate (**5**), formate (**6**), trifluoroacetate (**7**), and thioacetate (**8**). The choice was based on availability, ease of preparation for new applications, and possible biochemical utility.[6]

Two standardized procedures were developed. Method A involved the addition of a solution of the ester and *tert*-butyl alcohol in tetrahydrofuran (THF) to a solution of lithium in liquid ammonia. Method B involved the addition of lithium to a solution of the ester and *tert*-butyl alcohol in liquid ammonia–THF until the color of the reaction solution persisted blue. In both cases, after a standard work-up, the yield of toluene was determined by quantitative gas–liquid chromatography (glc). Since the conditions used (Li, NH_3, *t*-BuOH) can also reduce aromatic rings, it was necessary to consider product contamination by dihydro and tetrahydro derivatives of toluene. The absence of further reduced products was established by two procedures. A mixture of authentic samples of toluene, 1-methyl-1,4-cyclohexadiene, and 1-methylcyclohexene was cleanly resolved by glc analysis, and peaks corresponding to the latter two compounds were absent in the reaction mixture. Also, the hydrocarbon product from the reduction of benzyl acetate by method A was isolated by preparative glc; its nmr spectrum confirmed the presence of toluene exclusively.

The results are summarized in Table I. Method A was developed using a 20% excess of lithium based on the stoichiometry of 2 equiv of lithium per equivalent of ester. Under these conditions only the reductions of **3**, **5**, and **6** proceeded with preservation of the blue color throughout

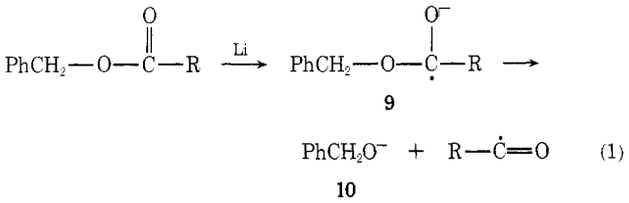
Table I
Reduction of Benzylic Esters (YCH_2Ph) by Lithium in Liquid Ammonia

Compd	Y	Toluene, %[a] Method A[b]	Method B	Li[c]
3	CH_3CO_2-	72	77	25
4	$C_6H_5CO_2-$	30	45	43
5	H_2NCO_2-	77	74	24
6	HCO_2-	67	66	28
7	CF_3CO_2-	51	57	29
8	CH_3COS-	26	83	43

[a] Average value (±2%) of duplicate runs. [b] Ester (10 mmol) added to lithium (24 mg-atoms). [c] Milligram-atoms of lithium added to ester (10 mmol) in order to generate blue reaction solution in method B.

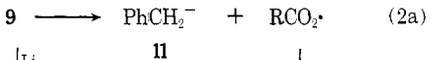
the addition of ester. After attempts to dissolve sufficient lithium for **4**, **7**, and 8 proved unpredictable, method B was employed. This inverse addition procedure proved to be the method of choice for the ease by which appropriate amounts of lithium could be regulated. A further advantage of method B was evident in the smooth and controllable reduction of **5**; this same reaction by method A was exceedingly vigorous. The tabulated data show that method B was equal or superior to method A in all cases studied.

Since no mechanistic studies have been reported for the dissolving metal reductions of allylic or benzylic esters, a few exploratory reactions were included in the present work. Three pathways for the reductive cleavage are possible. The first two routes proceed *via* anion radical **9**, which

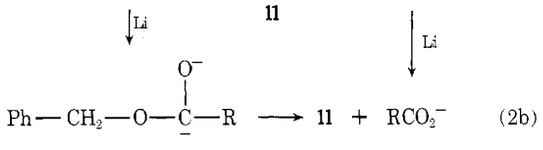


9

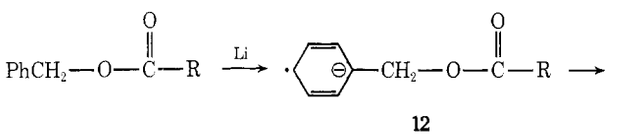
10 (1)



11 (2a)



(2b)



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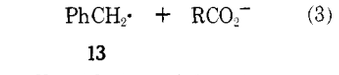

13 (3)

can cleave to generate either alkoxide ion **10** (eq 1), the initial phase of the acyloin condensation,[7] or carbanion **11** (eq 2a), the route postulated by Henbest, *et al.*,[3] for allylic acetates. The dianion in eq 2b represents an alternate precursor of **11**. Initial reduction of the aromatic ring (eq 3) can generate an anion radical suitable for fragmentation to radical **13** which, in turn, would be rapidly reduced to **11**. The chief distinction among these routes centers on whether the key intermediate is an alkoxide ion (**10**) or a carbanion (**11**). In the presence of a proton donor (*t*-BuOH) the generation of **10** would lead to benzyl alcohol (**14**), which can be reduced to toluene.[7] In a separate experiment under the conditions of method A **14** as reactant was converted to toluene in 89% yield. An attempt was made to differentiate between eq 1 and eq 2 or 3 by omitting the *tert*-butyl alcohol and quenching with sodium benzoate or ammonium chloride.[8] The use of sodium benzoate was designed to quench excess lithium and to preserve a benzylic alkoxide in the absence of an external proton source.[9] When applied to **3** this procedure afforded both toluene (14%) and **14** (8%) in low yield. A similar reduction (without added *t*-BuOH) of **3** when quenched with ammonium chloride also produced toluene (30%) and **14** (5%). These results are ambiguous and do not permit a single pathway to be deduced. The production of toluene in the absence of *tert*-butyl alcohol, regardless of the quenching reagent, is consistent with a carbanion intermediate. Alternatively, **10** could be protonated and the resulting **14** reduced to toluene before all of the excess lithium was quenched.[9] Finally, the low yields of toluene in the absence of added *tert*-butyl alcohol support initial ring reduction. It is possible, of course, that not all six esters follow the same pathway. Since the present work was carried out to establish the utility of dissolving metal reductions for the reductive cleavage of benzylic esters, no further studies are planned on the mechanistic aspects.

Experimental Section

Boiling points are uncorrected. Nmr spectra were recorded on a Perkin-Elmer R12B spectrometer, with CCl_4 as solvent and tetramethylsilane as internal standard. Preparative glc separations were performed on an Aerograph A-90-P instrument, fitted with a 0.375 in. × 20 ft column of 20% DC-710 on Chromosorb G.

Materials. Lithium wire (Alfa, 99.9%, 3.2 mm diameter) was stored under anhydrous benzene. Tetrahydrofuran (THF) was distilled from lithium aluminum hydride; a middle fraction was collected and stored under a nitrogen atmosphere. Commercial samples of **3**, **4**, and **6** were distilled *in vacuo* and middle fractions were collected; **5** was used as received. Esters **7** and **8** were prepared by published procedures: **7**[10] (81%), bp 72.3–73.0° (11 mm) [lit.[11] bp 50–52° (5 mm)]; **8**[12] (51%), bp 110–112° (8 mm) [lit.[13] bp 109° (5 mm)]. Samples of 1-methyl-1,4-cyclohexadiene and 1-methylcyclohexene (both 99%) were obtained from Chemical Samples Co.

Dissolving Metal Reduction. Method A. A 50-ml three-neck flask fitted with a Dry Ice–acetone condenser, mechanical stirrer, and gas inlet tube was flushed with argon and immersed in a Dry Ice–acetone bath. Gaseous ammonia was passed through a tower of potassium hydroxide pellets and *ca.* 20 ml was condensed in the flask. To a stirred solution of lithium (0.165 g, 24 mmol, washed and cut under anhydrous diethyl ether) in liquid ammonia was added dropwise from an argon-swept addition funnel a solution of the ester (10 mmol) and *tert*-butyl alcohol (0.74 g, 10 mmol) in THF (5 ml). After the addition was complete (*ca.* 10 min) the dark blue reaction solution was stirred for an additional 30 min, the excess lithium was quenched with solid ammonium chloride, the Dry Ice–acetone bath was removed, and the reaction mixture was allowed to warm to room temperature. After evaporation of the ammonia the flask was chilled in an ice bath, water (5 ml) was added, and the mixture was transferred to a separatory funnel and extracted twice with 7-ml portions of chloroform. The combined extract was washed once with 2 *N* hydrochloric acid and twice with saturated sodium chloride solution, dried over sodium sulfate, filtered into a 25-ml volumetric flask, and diluted to the mark with chloroform. This solution was analyzed by glc.

Method B. A 50-ml three-neck flask fitted as above was flushed with argon and immersed in a Dry Ice–acetone bath. To liquid ammonia (*ca.* 20 ml, condensed as above) was added a solution of the ester (10 mmol) and *tert*-butyl alcohol (0.74 g, 10 mmol) in THF (5 ml). To the stirred reaction solution was added lithium (*ca.* 4-mm lengths of wire washed and cut under diethyl ether) from an argon-swept 10-ml erlenmeyer flask connected to a side arm of the flask by Gooch tubing. Excess lithium was initially placed in the erlenmeyer flask and the actual amount used was determined by difference after sufficient lithium was added slowly (*ca.* 90 min) to generate a persistent dark blue solution. The color was discharged by

the addition of solid ammonium chloride, and the subsequent work-up procedure was the same as above.

Glc Analysis. Analysis of the chloroform solutions of toluene (prepared in 25-ml volumetric flasks) was conducted on a Varian 1420 instrument with a 0.125 in. × 10 ft column of 10% Dow Corning 710 on Chromosorb W, helium flow rate of 30 ml/min, and column temperature of 100°. The following retention times (in minutes) were observed: 1-methylcyclohexene, 3.7; toluene, 4.6; 1-methyl-1,4-cyclohexadiene, 5.2; benzyl alcohol, 37. Each product solution was analyzed in triplicate using a fixed-volume injection and the average peak height was related to millimoles of toluene by a least-squares computer plot of peak heights *vs.* known concentrations of toluene. The precision of this method was ±1%. Each reduction was carried out at least twice and the data in Table I are average values (±2%).

A control experiment in which a solution of toluene (10 mmol) and *tert*-butyl alcohol (10 mmol) in THF was added to a solution of lithium (3 mg-atoms) in liquid ammonia and the reaction solution was subjected to the standard work-up and glc analysis established that 90% of the toluene was recovered.

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Registry No.—**3,** 140-11-4; **4,** 120-51-4; **5,** 621-84-1; **6,** 104-57-4; **7,** 351-70-2; **8,** 32362-99-5; lithium, 7439-93-2.

References and Notes

(1) (a) Presented at the 5th Northeast Regional Meeting of the American Chemical Society, Rochester, N. Y., Oct 1973; (b) based on the Honors Thesis of L. I. Shoer, Williams College, 1973.
(2) J. H. Markgraf, S. J. Basta, and P. M. Wege, *J. Org. Chem.*, **37**, 2361 (1972).
(3) A. S. Hallsworth, H. B. Henbest, and T. I. Wrigley, *J. Chem. Soc.*, 1969 (1957).
(4) W. H. Hartung and R. Simonoff, *Org. React.*, **7**, 263 (1953).
(5) L. E. Khoo and H. H. Lee, *Tetrahedron Lett.*, 4351 (1968).
(6) J. P. Greenstein and M. Winitz, "Chemistry of the Amino Acids," Vol. 2, Wiley, New York, N. Y., 1961, pp 1239–1243.
(7) H. Smith, "Organic Reactions in Liquid Ammonia, Chemistry in Anhydrous Liquid Ammonia," Vol. 1, Wiley, New York, N. Y., 1963, Part 2, pp 160–161, 173–181.
(8) We thank a referee for assistance with the mechanistic interpretations.
(9) (a) S. S. Hall, S. D. Lipsky, and G. H. Small, *Tetrahedron Lett.*, 1853 (1971); (b) S. S. Hall, S. D. Lipsky, F. J. McEnroe, and A. P. Bartels, *J. Org. Chem.*, **36**, 2588 (1971).
(10) V. T. Oliverio and E. Sawicki, *J. Org. Chem.*, **20**, 363 (1955).
(11) A. C. Pierce and M. M. Joullie, *J. Org. Chem.*, **27**, 3968 (1962).
(12) A. A. Chilingaryan, Y. Y. Usaevich, and A. Y. Nazarov, *Tr. Leningrad. Khim.-Farm. Inst.*, 5 (1962); *Chem. Abstr.*, **60**, 10541*i* (1964).
(13) B. Wladislaw, H. Viertler, and E. B. Demant, *J. Chem. Soc. B*, 565 (1971).

Thiophenyl Malonate. A New Synthesis

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We wish to report a convenient procedure for synthesizing thiophenyl malonate, the active ester of choice for forming malonyl coenzyme A, based upon the reaction of malonic acid monochloride with thiophenol. We were led to develop this synthesis when we discovered that scaling up the normal procedure of Trams and Brady,[1,2] which involves coupling malonic acid with thiophenol using dicyclohexylcarbodiimide, produced no thiophenyl malonate but only a bright orange crystalline side product. In addition we had observed that some preparations of malonyl coenzyme A obtained from thiophenyl malonate synthesized by the Trams and Brady procedure were inexplicably one-half to one-third as active as others when used as substrate in enzymatic synthesis of fatty acids, indicative of the possible presence of inhibitory by-products.

The thiol ester obtained in low (13%) yield from the reaction of acid chloride with thiophenol is a colorless, stable solid. Using this material, a 10-mg sample of coenzyme A (approximately 10 μmol) yields about 8 μmol of malonyl coenzyme A.[1] The malonyl coenzyme A produced is fully active in reactions catalyzed by pigeon liver and rabbit mammary fatty acid synthetases as assayed spectrophotometrically in the presence of acetyl coenzyme A and NADPH.

Malonic Acid Monochloride. Malonic acid (15.6 g, 0.15 mol) and thionyl chloride (18 g, 0.15 mol) in 60 ml of ether were heated under reflux for 6 hr with stirring in a flask surmounted with a condenser and drying tube. During the reflux period, evolution of hydrogen chloride was observed. The solvent was then removed on a rotary evaporator under vacuum, and the remaining solid was triturated at 40° with ten 30-ml portions of a 1:2 mixture of chloroform–hexane. The combined extract was cooled to −15° and allowed to crystallize. The yellow crystals (5.27 g, 28.7%) of malonic acid monochloride were washed with hexane and dried overnight under vacuum, mp 58–61° (lit.[3] mp 63–65°).

Thiophenyl Malonate (Shirley's Ester). Thiophenol (1.9 g, 0.017 mol) was added dropwise to a stirred solution of 2.1 g (0.015 mol) of malonic acid monochloride in 25 ml of ether under an atmosphere of dry argon. The reaction was allowed to continue for 3 hr, after which time the solvent was removed on a rotary evaporator, leaving a moist solid which was placed under a vacuum of 0.1 mm until no more yellowish oil (thiophenol) could be observed. The majority of the solid was then dissolved in a minimum amount of chloroform and filtered to provide a clear yellow solution. Addition of hexane to the cloud point and subsequent cooling resulted in crystallization, providing a yellow solid, mp 57–68°. Dissolution in chloroform, decolorization with carbon, addition of hexane, and cooling in a Dry Ice–acetone bath provided 0.37 g (13%) of colorless crystals of thiophenyl malonate, mp 69–71° (lit.[2] mp 72–73°), which were collected and dried under vacuum: nmr ($CDCl_3$) δ 3.70 (s, 2 H), 7.42 (s, 5 H), 10.73 (s, 1 H); mass spectrum (80 eV) *m/e* (rel intensity) 196 (0.1, M^+), 152 (1.4, $M^+ - CO_2$), 110 (100, $PhSH^+$); ir (KBr) 1690 (O=CS), 1718 cm^{-1} (O=CO).

Anal. Calcd for $C_9H_8O_3S$: C, 55.09; H, 4.11; S, 16.34. Found: C, 54.79; H, 4.30; S, 16.61.

Registry No.—Malonic acid monochloride, 51932-41-3; malonic acid, 141-82-2; thionyl chloride, 7719-09-7; thiophenyl malonate, 4279-77-0; thiophenol, 108-98-5.

References and Notes

(1) E. G. Trams and R. O. Brady, *J. Amer. Chem. Soc.*, **82**, 2972 (1960).
(2) J. C. Howard, M. C. Lin, P. Matthews, and S. A. Singal, *J. Med. Chem.*, **8**, 888 (1965).
(3) H. Eggerer and F. Lynen, *Biochem. Z.*, **335**, 519 (1962).