**Registry No.**—1a, 3816-83-9; 1b, 14032-66-7; 1c, 766-40-5; 2b, 41473-30-7; 2c, 26212-26-0; 2d, 41473-32-9; 2e, 40125-53-9; 2f, 14032-71-4; 2g, 41473-35-2; 3, 41473-36-3; 5, 3712-44-5; 8a, 41473-38-5; 8b, 41611-40-9; 8c, 41473-39-6; 9a, 41473-40-9; 9b, 41473-41-0; 11, 26212-27-1; 11 picrate, 41473-42-1; 12a, 41473-43-2; 12a isomer, 41473-44-3; 12b, 41473-45-4; 12c, 41611-41-0; 12d, 41473-46-5; 13, 26212-28-2; 2,4-dimethoxypyrimidine, 3551-55-1.

# Reductive Alkylation of Monoaromatic Ketones

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Metal–ammonia reduction of acetophenone in the presence of *tert*-butyl alcohol is shown to proceed in three ways: dimerization to give *dl*-2,3-diphenylbutane-2,3-diol (**3**), nuclear reduction to form 1-(cyclohexa-2,5-dienylidene)ethanolate (enolate) (**4**), and carbonyl carbon reduction to yield 1-phenethyl alcohol. Subsequent *in situ* methylation of **4** generates 1-acetyl-1-methylcyclohexa-2,5-diene (**1**) and/or 1-(cyclohexa-2,5-dienylidene)-ethyl methyl ether (**5**), a hypothetical intermediate; the latter is supposed to isomerize to 1-phenethyl methyl ether. The product composition depends strongly upon the dissolving metal and methylating conditions used, and is controlled by proper selection of them; thus, reduction in ammonia–THF at −78° with potassium in either order of addition gives potassium enoate **4c** and subsequent methylation with methyl iodide in THF of lithium enolate **4b**, prepared by treatment of **4c** with lithium bromide, affords a regioselective preparative method of compound **1** in yields of >80%. Applicability of the method is established in reductive methylation of *o*-methoxyacetophenone (**6a**), *m*-methoxyacetophenone (**6b**), *p*-methylacetophenone (**6d**), and 1-tetralone. Similarly, 1-acetyl-1-ethylcyclohexa-2,5-diene (**10a**), 1-acetyl-1-allylcyclohexa-2,5-diene (**10b**), ethyl 1-acetylcyclohexa-2,5-dienylacetate (**10c**), and 1-acetylcyclohexa-2,5-dienylacetonitrile (**10e**) were prepared by using ethyl iodide, allyl bromide, ethyl bromoacetate, and chloroacetonitrile as the alkylating agent, respectively. HMO calculation suggests that the difference in the regioselectivity of the reduction according to the kind of counterion can be correlated with changes in electron density of the acetophenone dianion **12** on association with the counterion.

A solution of an alkali metal in ammonia combined with a proton source has long been known to provide an efficient reducing system[1] for aromatic rings. Partial nuclear reduction of benzoic acids by this method to give 1,4-dihydro derivatives as the primary products has been well established.[2,3] It has since been found[3,4] that the reduction can proceed without addition of a proton source, the intermediate enolates being subsequently alkylated *in situ* to afford 1-alkyl-1,4-dihydrobenzoic acids.

Metal–ammonia reduction of aromatic ketones takes a different course:[1] the site of reduction is always localized at the carbonyl carbon. Reduction of acetophenone in liquid ammonia with an excess of potassium and *tert*-butyl alcohol gives ethylbenzene,[5,6] while benzophenone is reduced with sodium in ammonia followed by quenching with water to give diphenylmethanol.[7,8] Conversion of benzophenone, 1-tetralones, and 1-indanones into aromatic hydrocarbons by an excess of lithium[3] in liquid ammonia and ammonium chloride quench has been recently reported.[9] Electrophilic reaction on the benzophenone dianion, produced with an equivalent amount of metal in liquid ammonia, resulting in formation of diphenylmethane derivatives has been investigated in detail.[10]

The apparent difficulty of nuclear reduction of aromatic ketones compared with the smooth nuclear reduction in the benzoic acid series attracted our attention and prompted us to investigate the problem.

We now report our findings that under selected conditions metal–ammonia reduction of acetophenone proceeds by the hitherto unknown nuclear reduction[11–13] and that after cation exchange of the counterion the resulting enolate is selectively methylated *in situ*

(1) For general discussions, see (a) A. J. Birch, *Quart. Rev., Chem. Soc.*, **4**, 69 (1950); (b) A. J. Birch and H. Smith, *ibid.*, **12**, 17 (1958); (c) G. W. Watt, *Chem. Rev.*, **46**, 317 (1950); (d) C. Djerassi, Ed., "Steroid Reactions," Holden-Day, San Francisco, Calif., 1963; (e) H. Smith, "Organic Reactions in Liquid Ammonia, Vol. 1, Part 2, Chemistry in Nonaqueous Ionizing Solvents," Wiley, New York, N. Y., 1963; (f) R. L. Augustine, "Reduction: Techniques and Applications in Organic Synthesis," Marcel Dekker, New York, N. Y., 1968; (g) H. O. House, "Modern Synthetic Reactions," 2nd ed, W. A. Benjamin, Menlo Park, Calif., 1972; (h) R. G. Harvey, *Synthesis*, 161 (1970); (i) E. M. Kaiser, *ibid.*, 392 (1972).

(2) (a) A. J. Birch, *J. Chem. Soc.*, 1551 (1950); (b) A. J. Birch, P. Hextall, and S. Sternhell, *Aust. J. Chem.*, **7**, 256 (1954); (c) H. Plieniger and G. Ege, *Angew. Chem.*, **70**, 505 (1958); (d) M. E. Kuehne and B. F. Lambert, *J. Amer. Chem. Soc.*, **81**, 4278 (1959); (e) A. P. Krapcho and A. A. Bothner-By, *ibid.*, **81**, 3658 (1959); (f) O. L. Chapman and P. Fitton, *ibid.*, **83**, 1005 (1961); **85**, 41 (1963); (g) F. Camps, J. Coll, and J. Pascual, *J. Org. Chem.*, **32**, 2563 (1967); (h) M. E. C. Biffin, A. G. Moritz, and D. B. Paul, *Aust. J. Chem.*, **25**, 1329 (1972).

(3) (a) M. D. Bachi, J. W. Epstein, Y. Herzberg-Minzly, and H. J. E. Loewenthal, *J. Org. Chem.*, **34**, 126 (1969); (b) H. van Bekkem, C. B. van den Bosch, G. van Minnenpathuis, J. C. de Mos, and A. M. van Wijk, *Recl. Trav. Chim. Pays-Bas*, **90**, 137 (1971).

(4) For similar reductive methylation of biphenyl and polynuclear aromatic compounds, see D. F. Lindow, C. N. Cortez, and R. G. Harvey, *J. Amer. Chem. Soc.*, **94**, 5406 (1972), and the papers in this series.

(5) A. R. Pinder and H. Smith, *J. Chem. Soc.*, 113 (1954).

(6) Metal was added to the ketone solution.

(7) (a) H. Schlubach, *Chem. Ber.*, **48**, 12 (1915); (b) See also W. E. Bachmann, *J. Amer. Chem. Soc.*, **55**, 1179 (1933).

(8) Ketone was added to the solution of metal in ammonia.

(9) (a) S. S. Hall, S. D. Lipsky, F. J. McEnroe, and A. P. Bartels, *J. Org. Chem.*, **36**, 2588 (1971). The accelerating effect of a catalytic amount of cobalt or aluminum was observed. (b) S. S. Hall, S. D. Lipsky, and G. H. Small, *Tetrahedron Lett.*, 1853 (1971).

(10) (a) P. J. Hamrick, Jr., and C. R. Hauser, *J. Amer. Chem. Soc.*, **81**, 493 (1959); (b) S. Selman and J. F. Eastham, *J. Org. Chem.*, **30**, 3804 (1965); (c) E. L. Anderson and J. E. Casey, Jr., *ibid.*, **30**, 3955 (1965); (d) W. S. Murphy and D. J. Buckley, *Tetrahedron Lett.*, 2975 (1969).

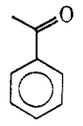
(11) Pinder and Smith[5] have already attempted to prepare 1-acetylcyclohexa-2,5-diene by potassium–*tert*-butyl alcohol–ammonia reduction of the potassium enolate of acetophenone, an equivalent to benzoate, but they recovered acetophenone.

(12) For the lithium–methylamine reduction of acetophenone yielding 1-(cyclohexen-1-yl)ethanol, see (a) R. A. Benkeser, C. Arnold, Jr., R. F. Lambert, and O. H. Thomas, *J. Amer. Chem. Soc.*, **77**, 6042 (1955); (b) R. A. Benkeser, R. K. Agnihotri, M. L. Burrous, E. M. Kaiser, J. M. Mallan, and P. W. Ryan, *J. Org. Chem.*, **29**, 1313 (1964).

(13) Reduction of pivalophenone by magnesium–trimethylsilyl chloride to 1-(*p*-trimethylsilylphenyl)-2,2-dimethylpropane trimethylsilyl ether *via* initial nuclear reduction and subsequent aromatization has been reported. See (a) R. Calas, C. Biran, J. Dunogues, and N. Duffaut, *C. R. Acad. Sci., Ser. C*, **269**, 412 (1969); (b) R. Calas, J. Dunogues, J.-P. Pillot, C. Biran, and N. Duffaut, *J. Organometal. Chem.*, **25**, 43 (1970); (c) J.-P. Pillot, J. Dunogues, R. Calas, and N. Duffaut, *Bull. Soc. Chim. Fr.*, 3490 (1972).

TABLE I

REDUCTIVE METHYLATION OF ACETOPHENONE[a]



1. M/proton source/$NH_3$–THF/−78°, 10 min
2. LiX/$NH_3$–THF/−78°, 40 min
3. $CH_3I$/THF/0–10°, 40 min

→ products

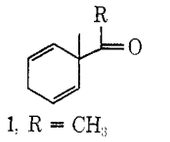
| Item No. | Metal | Proton source | Molar equiv | Lithium halide | Yield of product, %[b] Ethylbenzene | 1-Phenethyl methyl ether | 1 | 2 | Acetophenone | Isobutyrophenone | Propiophenone | 1-Phenethyl alcohol | 3 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Li | HOAc | 1.0 | | <3[c] | 2 | 41 | 1 | 3 | 1 | 2 | 18 | 19[c] |
| 2 | Li | $H_2O$ | 1.1 | | <3[c] | 1 | 21 | | 4 | 2 | 2 | 47 | 11[c] |
| 3 | Li | *t*-BuOH | 1.2 | | 8[c] | 6 | 26 | 5 | 6 | 6 | <1 | 19 | 8[d] |
| 4 | Li | *t*-BuOH | 6.0 | | 4[c] | 3 | 36 | 2 | 4 | 5 | 12 | 23 | <3[c] |
| 5 | Na | *t*-BuOH | 1.2 | | 3[c] | 23 | 12 | 25 | | 4 | | 8 | 3[d] |
| 6 | Na | *t*-BuOH | 6.0 | | | 34 | 14 | 28 | | 2 | | 9 | <3[c] |
| 7 | Na | *t*-BuOH | 1.2 | LiI | 9[c] | <1 | 53 | | 1 | | | 14 | <3[c] |
| 8 | Na | *t*-BuOH | 1.2 | LiBr | | <1 | 61 | | 4 | | | 21 | <3[c] |
| 9[e] | Na | *t*-BuOH | 6.0 | LiI | 4[c] | <1 | 46 | 1 | 1 | | | 36 | <3[c] |
| 10 | Na | | | LiI | 11[c] | <1 | 26 | | 1 | | | 16 | 35[c] |
| 11 | K | *t*-BuOH | 1.2 | LiBr | 7[c] | <1 | 84 | | 5 | | | 2 | 3[d] |
| 12 | K[f] | *t*-BuOH | 0.5 | | | | 25 | 2 | 22 | 17 | 4 | | 13[d] |

[a] Procedure is described in the Experimental Section. [b] Determined by glpc analysis unless otherwise stated. [c] Based on nmr spectroscopy. [d] Isolated by alumina chromatography. [e] Reduction was carried out at −33°. [f] 1.0 atom equiv of potassium was used.

to produce 1-acetyl-1-methylcyclohexa-2,5-diene (**1**). The mechanism of the reaction and application for preparation of derivatives of **1** are also described.

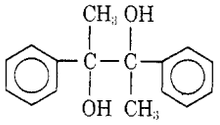
## Results and Discussion

**Reductive Methylation of Acetophenone.**—The product mixture from reductive methylation of acetophenone consists of ethylbenzene, 1-phenethyl methyl ether, 1-acetyl-1-methylcyclohexa-2,5-diene (**1**), 1-isobutyryl-1-methylcyclohexa-2,5-diene (**2**), acetophenone, isobutyrophenone, propiophenone, 1-phenethyl alcohol, and *dl*-2,3-diphenylbutane-2,3-diol (**3**). The

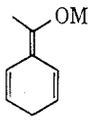


1, R = $CH_3$

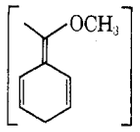
2, R = $CH(CH_3)_2$



**3**



**4a**, M = Na
**b**, M = Li
**c**, M = K



**5**

1,4-dihydro structure of **1** is easily assigned, mainly from the presence in the nmr spectrum of proton signals characteristic of a symmetrical diene group (4 H, δ 5.53 and 5.86), an acetyl group (3 H, δ 2.12), and a $CH_3C<$ group (3 H, δ 1.22). Structures of other products were deduced from their nmr spectra and confirmed by identification with authentic samples.

Investigation into the factors influencing product composition gave interesting results (Table I). In each experiment reduction proceeded, giving some amount of **1**, regardless of the nature of the proton source and the kind of metal. It was initially assumed that use of a strongly acidic proton source would be necessary for the reduction, judging from the fact that benzoic acids are reduced smoothly to the 1,4-dihydro derivatives with alkali metal and their own protons.[3,14] However, it turned out that *tert*-butyl alcohol (1.2 or 6.0 molar equiv) behaves as a satisfactory proton source. A significant increase in the amount of **3** was observed when acetic acid was used as the proton source (compare item 1 with 3 and 4). Also, water assisted the preferential formation of 1-phenethyl alcohol (item 2).

A profound effect on the reaction pattern was observed on substitution of sodium for lithium: methylation of **1** was enhanced with an increase in the yield of **2**, recovery of the starting material and its methylated compounds was decreased, production of 1-phenethyl alcohol was suppressed, and dominant formation of 1-phenethyl methyl ether was observed (items 5 and 6). The last fact may be interpreted by assuming that the methyl ether is generated through O-methylation of intermediate sodium trienolate **4a** and subsequent aromatization of the resulting methyl enolate **5**, and this was verified by the fact that methyl ether formation became negligible and the yield of compound **1** was increased when, in order to avoid[15] the O-methylation, an attempt was made to convert sodium enolate **4a** into lithium enolate **4b** by additional treatment with lithium

(14) The authors are grateful to a referee who has called their attention to a report that sodium benzoate very rapidly quenches lithium dissolved in ammonia in the presence of ethanol[2c] (and without a proton source[2g]). In fact, sodium benzoate was reduced with 1.9 molar equiv of lithium in ammonia–THF without added proton source at −78° and successively methylated with methyl iodide to give 1-methylcyclohexa-2,5-dienecarboxylic acid in 56% yield after distillation as its methyl ester (unpublished data). However, since base-catalyzed isomerization and further reduction of a 1,4-dihydrobenzoic acid has been reported,[2b,h] we have considered that, in addition to the protonation, quenching of sodium amide may be important in preventing the possible isomerization of 1,4-dihydroacetophenone to phenethyl alcohol.

(15) For general discussion on the problem of O-methylation and C-methylation of ambident anions, see (a) R. Gomper, *Angew. Chem.*, **76**, 412 (1964); *Angew. Chem., Int. Ed. Engl.*, **3**, 560 (1964); (b) W. J. Le Noble, *Synthesis*, 1 (1970); (c) Reference 1g.

iodide (item 7). In addition, the undesirable methylation yielding **2** was also suppressed by this treatment. Lithium bromide showed a similar effect (item 8), while lithium chloride was unsatisfactory.

Several additional factors were also found: reverse order[16] of addition of lithium and sodium caused a slightly dimenished yield of **1**; a significant temperature effect was seen, formation of 1-phenethyl alcohol was increased at an elevated temperature (item 9); and reduction without a proton source resulted in increased accumulation of the pinacol **3** (item 10).

Optimal conditions were obtained when acetophenone was treated in a selected combination of metals (item 11). Thus, compound **1** was isolated in 80% yield after fractional distillation. Contrary to the experiments using lithium and sodium, reverse addition[16] in the reduction with potassium gave a slightly increased yield (90%). Reduction using a twofold excess of potassium (4.0 instead of 2.2 atom equiv in item 11) under more drastic conditions (80 min at −33° in addition to 10 min at −78° in item 11) little affected the product composition.

**Reductive Methylation of Substituted Acetophenone.**—In Table II, examples of reductive methylation

TABLE II

REDUCTIVE METHYLATION OF ACETOPHENONE DERIVATIVES

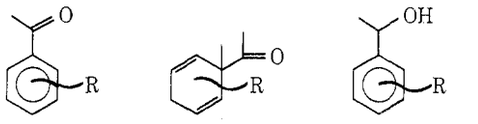
| Substrate | Product | Yield, % |
|---|---|---|
| **6a** | **7a** | 74[a] |
| **6b** | **7b** | 89[a] |
| **6c** | **1** | 33[b] |
| | **8a** | 16[b] |
| | **6c** | 37[b] |
| **6d** | **7c** | 55[b,c] |
| | **8b** | 26[b] |
| 1-Tetralone | **9** | 60,[a] 62[a,d] |
| | Tetralin | 4,[a] 1[a,d] (96[e]) |
| | 1-Tetralone | 13,[a] 14[a,d] |

[a] Isolated yield. [b] Based on glpc analysis. [c] A mixture of cis and trans isomers. [d] By reverse addition.[16] [e] See ref 9.

of acetophenone derivatives are listed. All the products gave satisfactory analytical and spectral data and the by-products were identified with authentic samples.

Of the methoxy acetophenones, ortho- and meta-substituted derivatives **6a** and **6b** were converted smoothly into compounds **7a** and **7b**, while the para-substituted compound **6c** suffered elimination resulting in **1**. Successful nuclear reduction of a para-substituted acetophenone was observed only with methyl derivative **6d**, a 1:1 mixture of cis and trans isomers **7c** being obtained. Both of the para-substituted derivatives underwent marked carbonyl reduction, producing alcohols **8a** and **8b**. Effective conversion of 1-tetralone into tetralin by reduction[8] with 5 molar equiv of lithium in ammonia–THF at reflux temperature and ammonium chloride quench has been reported.[9] By our procedure (reduction using 2.5 molar equiv of potassium in either order of addition and 3.0 molar equiv of *tert*-butyl alcohol in ammonia–THF at −78° and *in situ* methylation with methyl iodide in THF after treatment of lithium bromide), the nuclear reduction product **9** was obtained in yields of >60%. The formation of tetralin was substantially suppressed.

(16) Addition of a solution of ketone and a proton source to a solution of alkali metal in liquid ammonia.



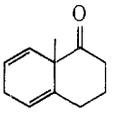
**6a**, R = *o*-$OCH_3$
**b**, R = *m*-$OCH_3$
**c**, R = *p*-$OCH_3$
**d**, R = *p*-$CH_3$



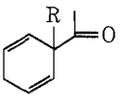
**7a**, R = *o*-$OCH_3$
**b**, R = *m*-$OCH_3$
**c**, R = *p*-$CH_3$
(a mixture of cis and trans isomers)



**8a**, R = *p*-$OCH_3$
**b**, R = *p*-$CH_3$



**9**



**10a**, R = $C_2H_5$
**b**, R = $CH_2CH{=}CH_2$
**c**, R = $CH_2COOC_2H_5$
**d**, R = $CH_2COOH$
**e**, R = $CH_2CN$

**Reductive Alkylation of Acetophenone.**—Utilizing the optimal conditions for the reductive methylation of acetophenone, compounds **10a, 10b, 10c, 10d,** and **10e** were prepared (Table III). Assignment of the structure of each compound was made from analytical and spectral data. Although the reaction conditions were not optimized, it is concluded that the reactive alkylating reagents alkylate lithium enolate **4b** satisfactorily. It is also noteworthy that attempts to alkylate it with chloroacetone, *n*-amyl bromide, and *p*-iodoanisole failed.

TABLE III

REDUCTIVE ALKYLATION OF ACETOPHENONE

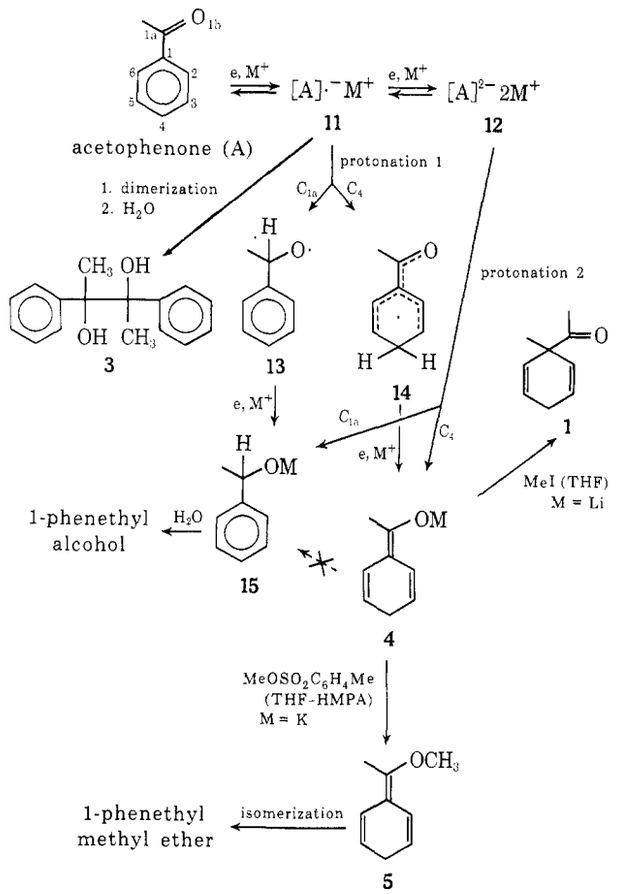
| Alkylating reagent | Product | Yield, % |
|---|---|---|
| $C_2H_5I$ | **10a** | 59[a] |
| $CH_2{=}CHCH_2Br$ | **10b** | 85[b] |
| $BrCH_2COOC_2H_5$ | **10c** | 62[a] |
| | **10d** | 21[b] |
| $ClCH_2CN$ | **10e** | 26[a] |

[a] Based on glpc analysis. [b] Isolated yield.

**Mechanism of Reductive Methylation of Acetophenone.**—Reductive methylation of acetophenone is rather complicated compared with that[3b] of benzoic acid. Scheme I shows a suggested mechanism for the important figures of the reaction.

The anion radical **11** formed by one-electron reduction of acetophenone is consumed in three ways: (1) dimerization to **3**; (2) protonation 1 to produce radicals **13** and **14** and then further reduction to give **15** and **4**; and (3) acceptance of a second electron to form the dianion **12**, which is transformed to alcoholates **15** and **4** by protonation 2. To obtain some idea of the competition between these alternative reactions, an experiment was carried out in which the reduction was stopped halfway (Table I, item 12). This showed a distinct increase in amount of the pinacol **3**. We consider this to imply that the reduction path *via* protonation 1 is not significant, otherwise half of the yield of compound **1** would be retained without any increase in the formation of **3**, and that an insufficiency of metal retards the consumption of **11** through **12**, resulting in formation of **3**. Evidence for the formation of the dianion **12** is also given by the observation of a deep green color in the reaction mixture where no proton source was added

SCHEME I




(Table I, item 10); the low concentration of proton retards the consumption of the dianion, making it observable. These pieces of evidence suggest that protonation 2 is the more important path.[17,18]

Protonation 2 is presumably a kinetically controlled process. Possible isomerization of lithium enolate **4b** to alcoholate **15** is excluded by the observation that almost pure lithium enolate **4b**, prepared by treatment of potassium enolate **4c** with lithium iodide, did not produce any detectable increase in the amount of 1-phenethyl alcohol but gave mainly **1** after prolonged stirring at −33° and subsequent methylation. Thus, the product ratios of compound **1** to 1-phenethyl alcohol are believed to reflect directly the relative rates of $C_4$ to $C_{1a}$ protonations, which increase rapidly in the order Li < Na < K (Table I, items 3, 8, and 11). Protonation during the Birch reduction of aromatic hydrocarbons is known to proceed in accord with HMO theory.[20] So we attempted to interpret the difference in the relative rates of protonation in terms of the changes in electron density of the dianion on association[21] with the counterion. In Table IV, the calculated values of electron densities and spin densities of the radical anion **11** and the dianion **12** are shown. Choice of the parameters is based on the work of Steinberger and Fraenkel,[22] who have shown a very good agreement of the calculated values with the experimental values of the spin densities of the free anion radical **11** in DMF. As parameters for the associated species, we used values[23,24] intermediate between those for the free species and for a hypothetical species which is protonated at the oxygen atom. The electron densities of the free and associated dianions agree[25] well with the observed decreasing trend of relative rates of $C_4$ to $C_{1a}$ protonations in the order K > Na > Li when covalencies of the bond between the oxygen atom and the alkali metals are supposed to increase in the order K < Na < Li.

TABLE IV

SPIN AND ELECTRON DENSITIES OF [A]·⁻ AND [A]²⁻

| | [A]·⁻ Spin densities[a] Free | [A]·⁻ Spin densities[a] Associated | [A]·⁻ Electron densities Free | [A]·⁻ Electron densities Associated | [A]²⁻ Electron densities Free | [A]²⁻ Electron densities Associated |
|---|---|---|---|---|---|---|
| 1 | 0.095 | −0.037 | 1.156 | 1.052 | 1.270 | 1.077 |
| 2 | 0.164 | 0.170 | 1.049 | 1.039 | 1.178 | 1.167 |
| 3 | −0.046 | −0.062 | 1.031 | 1.005 | 1.052 | 1.008 |
| 4 | 0.270 | 0.182 | 1.148 | 1.059 | 1.345 | 1.199 |
| 5 | −0.057 | −0.062 | 1.021 | 1.005 | 1.034 | 1.008 |
| 6 | 0.183 | 0.170 | 1.082 | 1.039 | 1.222 | 1.167 |
| 1a | 0.260 | 0.564 | 0.895 | 0.985 | 1.131 | 1.439 |
| 1b | 0.131 | 0.076 | 1.618 | 1.816 | 1.768 | 1.935 |

[a] McLachalan modification of Hückel calculation with λ = 1.2; see A. D. McLachalan, *Mol. Phys.*, **3**, 233 (1960).

Methylation of enolate **4** with methyl iodide proceeds in two ways depending on the sort of counterion. With lithium it is methylated exclusively at $C_1$ to afford compound **1**, while the sodium salt is methylated both at the oxygen atom and at $C_1$.[26] The O-methylation product **5** is believed to isomerize into 1-phenethyl methyl ether. Interestingly, potassium enolate **4c** was methylated to yield only a small amount of 1-phenethyl methyl ether. This might be ascribable to the low solubility of the enolate.[15] However, methylation of potassium enolate **4c** with methyl *p*-toluene-

(17) In the reduction employing a strongly acidic proton source, we still retain the possibility of the protonation 1 as a by-path.

(18) Polarographic study on the reduction of acetophenone in dimethylformamide has revealed that at a lower concentration of proton (less than 1 molar equiv of phenol) acetophenone is reduced to the radical anion **11** in a reversible manner and successively to the dianion **12** in an irreversible manner at −1.95 and −2.63 V[19] *vs.* a saturated calomel electrode, respectively, and that at a higher concentration of phenol protonation of the radical anion **11** becomes a diffusion-controlled competitive reaction path. See J. Simonet, *Bull. Soc. Chim. Fr.*, 1533 (1970). The facts are compatible with our suggested mechanism.

(19) The value is in the range −2.9 V or less (*vs.* a saturated calomel electrode) noted for the reduction potential of dissolving metals in ammonia.[1g]

(20) A. Streitwieser, Jr., "Molecular Orbital Theory for Organic Chemists," Wiley, New York, N. Y., 1961.

(21) (a) Zaugg and Schaefer have investigated the effects of cation and solvent on the uv spectra of alkali phenolates and enolates and showed that the $\pi$–$\pi^*$ transition energies in DMF are proportional to the inverse of the cationic radius. See H. E. Zaugg and A. D. Schaefer, *J. Amer. Chem. Soc.*, **87**, 1857 (1965). (b) Hogen-Esch and Smid observed increasing diametrically opposite cation effects (solvent-induced shifts on the uv spectra) of 9-fluorenyl salts in THF on lowering the temperature to −50°. See T. E. Hogen-Esch and J. Smid, *J. Amer. Chem. Soc.*, **88**, 307 (1966).

(22) N. Steinberger and G. K. Fraenkel, *J. Chem. Phys.*, **40**, 723 (1964).

(23) The values used[22] for the free ion ($\gamma_{CC}^* = 1.1$, $\delta_O = 1.55$, $\gamma_{CO} = 1.7$, and $\delta_{C'} = -0.05$) were modified to the following values for the associated ion: $\gamma_{CC}^* = 1.0$, $\delta_O = 2.05$, $\gamma_{CO} = 1.2$, $\delta_{C_{1a}} = 0.10$, and $\delta_{C'} = 0.00$.

(24) For a more precise treatment of the cation effect on esr spectra of aromatic nitro compounds at various temperatures, see Y. Kawamura, K. Nishikida, and T. Kubota, *Bull. Chem. Soc. Jap.*, **46**, 737 (1973), and references cited therein.

(25) The spin densities and the net charge at $C_{1a}$ of the anion radical are considered to parallel with the experimentally found tendency for dimerization.

(26) A referee kindly informed us of a report describing nmr evidence for the structure (solvent-separated ion pairs *vs.* contact ion pairs) of metal enolates in various solvents. Kinetically controlled acylation of the contact ion pairs gave the C-acylated products while that of solvent-separated ion pairs gave the O-acylated products. See H. O. House, R. A. Auerbach, M. Gall, and N. P. Peet, *J. Org. Chem.*, **38**, 514 (1973). These evidences accord with our mechanism.

sulfonate in a 1:2 mixture of THF–hexamethylphosphoric triamide (HMPA)[27] proceeded almost exclusively to give 1-phenethyl methyl ether in 63% yield and little **1**. The result supports strongly the above-described hypothesis for the formation of 1-phenethyl methyl ether *via* **5**. An alternate path for the formation of 1-phenethyl methyl ether by methylation of **15** cannot be excluded but must be of minor contribution on the basis of the composition change on lithium halide treatment.

The importance of the species of counterion for control of the reductive methylation of acetophenone was revealed. Selecting a suitable species of counterion in each step, an efficient preparative method of compound **1** is established. Synthetic applicability of the method for similar compounds is also shown. The importance in nuclear and the carbonyl reduction of the changes in electron density of the intermediate acetophenone dianion owing to counterion association is also suggested.

## Experimental Section

**Physical Data.**—Gas chromatographic analyses were performed on a Shimazu GC-4A chromatograph employing a 1.5 m × 4 mm 1% Carbowax 20 M on Gas-Chrom Q column at 130° and 1.4 kg/cm² nitrogen pressure. Proton nmr spectra were recorded on a Varian A-60 spectrometer; chemical shifts are reported relative to TMS in $CDCl_3$. Ir spectra were obtained on a Jasco DS-403G grating spectrometer in $CHCl_3$, unless otherwise noted. Mass spectra were measured on a Hitachi RMU-6 mass spectrometer at 70 eV.

**Reductive Methylation of Acetophenone. General Procedure.**—All the reactions were carried out under slight pressure of dry nitrogen.[28] Tetrahydrofuran (THF) was purified by refluxing under nitrogen over sodium hydride and distilled just before use. Dry ammonia[29] (140 ml) was placed in a flask equipped with a ground glass seal stirrer and cooled at −78°. A solution of 5.192 g (43.2 mmol) of acetophenone and a proton source (1.0–6.0 × 43.2 mmol) diluted with 20 ml of THF was introduced, followed by small pieces of alkali metal (2.2–2.5 × 43.2 mg-atoms) with efficient stirring over a period of 1–5 min. The resulting mixture was then stirred for 10 min; usually the initially observed blue color persisted. The resulting blue solution was in some cases (Table I, items 7, 8, 9, 10, and 11) mixed with anhydrous lithium halide (2.2 × 43.2 mmol) and stirred at −78° for 40 min; in other cases (Table I, items 1, 2, 3, 4, 5, 6, and 12) this operation was omitted. The ammonia was evaporated during 1–4 hr and the resulting pasty mixture was methylated by adding methyl iodide (2.0 × 43.2 mmol) and stirring the mixture at 0–10° for 40 min. Saturated salt solution and ether were added to the reaction mixture and the resulting two-phase solution was adjusted to pH 7.5 by cautious addition of hydrochloric acid at 0°. The ether layer was separated and the aqueous layer was extracted with ether. The organic layer was washed with salt solution and dried over sodium sulfate, and the solvent was evaporated under reduced pressure at room temperature. Yields of each component were determined by glpc analysis employing phenethol as internal standard; retention times of 1-phenethyl methyl ether, phenethole, **1**, **2**, acetophenone, isobutyrophenone, and propiophenone were 0.68, 0.78, 1.08, 1.38, 2.65, 3.43, and 3.65 min, respectively. The product ratios of ethyl benzene and **3** relative to 1 were determined by repeated measurements of the integrated areas (on a Varian T-60) of the signals characteristic for each component. The yield of **3** was also confirmed by isolation by alumina column chromatography, the value agreeing well with that obtained by nmr spectroscopy.

*dl*-**2,3-Diphenylbutane-2,3-diol** (**3**)[30,31] had mp 125–127° (lit.[30] mp 122–124°); $\nu$ ($CCl_4$) 3628, 3581, 1603, 1495, 1442, 1373, 1355, and 1143 cm⁻¹ (lit.[30] 1355 and 1143 cm⁻¹ as characteristic bands to the *dl* form). *Anal.* Calcd for $C_{16}H_{18}O_2$: C, 79.31; H, 7.49. Found: C, 79.42; H, 7.47. Nmr $\delta$ 1.46 (6 H, s), 2.66 (2 H, broad s), and 7.17 (10 H, s).

**1-Acetyl-1-methylcyclohexa-2,5-diene** (**1**).—Under optimal conditions (Table I, item 11), **1** was isolated in a yield of 80% after fractional distillation of the above-described mixture, bp 72.2° (18 mm), $n^{18.5}$D 1.4802. *Anal.* Calcd for $C_9H_{12}O$: C, 79.37; H, 8.88. Found: C, 79.10; H, 8.75. Ir $\nu$ 1707, 1673, 1632, and 1602 cm⁻¹; mass spectrum *m/e* (rel intensity) 136 ($M^+$, 0.2), 94 (100), 92 (66), and 77 (52); nmr $\delta$ 1.22 (3, H s), 2.12 (3 H, s), 2.74 (2 H, m), 5.53 (2 H, d of t, $J$ = 10.5, 2.0 Hz), and 5.86 (2 H, d of t, $J$ = 10.5, 3.0 Hz).

**1-Isobutyryl-1-methylcyclohexa-2,5-diene** (**2**).—An authentic sample was prepared by methylation of **1**. To a solution of 38 ml of a 1.68 *M* solution of sodium *tert*-amylate in benzene diluted with 90 ml of THF, cooled at −10 to −13°, a mixture of 3.967 g of **1**, 9.13 g of methyl iodide, and 100 ml of THF was added dropwise under a nitrogen atmosphere. After introduction of an additional 2.08 g of methyl iodide, the resulting mixture was stirred at room temperature for 75 min. The resulting cloudy solution was poured into ice–water and extracted with ether. The product was shown to be almost pure **2** contaminated with a trace of the monomethylated product by nmr spectrum. After distillation, the sample was analyzed, bp 104° (33 mm). *Anal.* Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.83. Found: C, 80.05; H, 9.75. Ir $\nu$ 1704, 1671, 1630, and 1602 cm⁻¹; mass spectrum *m/e* (rel intensity) 121 (1.6) and 93 (100); nmr $\delta$ 1.00 (6 H, d, $J$ = 7.0 Hz), 1.21 (3 H, s), 2.77 (2 H, m), 3.15 (1 H, septet, $J$ = 7.0 Hz), 5.52 (2 H, d of t, $J$ = 10.5, 1.9 Hz), and 5.88 (2 H, d of t, $J$ = 10.5, 3.0 Hz).

**Reductive Methylation of Acetophenone Derivatives. A. Reductive Methylation of *o*-Methoxyacetophenone** (**6a**).—The reaction was carried out in a similar way to that described for the reductive methylation of acetophenone. A mixture of 10.026 g (66.6 mmol) of *o*-methoxyacetophenone, 7.55 ml (1.2 × 66.6 mmol) of dry *tert*-butyl alcohol, and 40 ml of THF was added under nitrogen[28] to 270 ml of redistilled ammonia[29] cooled at −78°. Small pieces of potassium (5.75 g, 2.2 × 66.6 mg-atom) were added quickly to the stirred mixture. After 10 min of stirring, 12.8 g (2.2 × 66.6 mmol) of anhydrous lithium bromide was added and the mixture was stirred at −78° for 40 min. The ammonia was evaporated to give a pasty mixture, to which 8.3 ml (2.0 × 66.6 mmol) of methyl iodide was injected and the resulting mixture was stirred vigorously at 0–10° for 40 min. The reaction mixture was diluted with salt solution and extracted with ether. The ether solution was washed with salt solution and dried over sodium sulfate, and the solvent was evaporated under reduced pressure. Distillation produced pure **1-acetyl-1-methyl-2-methoxycyclohexa-2,5-diene** (**7a**) in a yield of 74%, bp 67–70° (2.0 mm), $n^{25}$D 1.4848, $d^{25}25$ 1.0171. *Anal.* Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.44; H, 8.50. Ir $\nu$ 1713, 1683, 1644, and 1597 cm⁻¹; mass spectrum *m/e* (rel intensity) 166 ($M^+$, 4.5), 123 (91), 108 (100), and 91 (66); nmr $\delta$ 1.27 (3 H, s), 2.07 (3 H, s), 2.76 (2 H, m), 3.52 (3 H, s), 4.80 (1 H, t, $J$ = 3.5 Hz), 5.27 (1 H, d of t, $J$ = 10.0, 2.0 Hz), and 5.83 (1 H, d of t, $J$ = 10.0, 3.5 Hz).

**B. Reductive Methylation of *m*-Methoxyacetophenone** (**6b**).—In a way similar to A, *m*-methoxyacetophenone was treated to produce **1-acetyl-1-methyl-3-methoxycyclohexa-2,5-diene** (**7b**) in a yield of 89%, bp 69.5–71° (2.0 mm), $n^{25}$D 1.4856, $d^{25}25$ 1.0192. *Anal.* Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 71.97; H, 8.48. Ir $\nu$ 1710, 1681, and 1640 cm⁻¹; mass spectrum *m/e* (rel intensity) 166 ($M^+$, 1.5) and 108 (100); nmr $\delta$ 1.22 (3 H, s), 2.10 (3 H, s), 2.79 (2 H, m), 3.56 (3 H, s), 4.47 (1 H, $W_{1/2}$ = 3 Hz), 5.51 (1 H, d of q, $J$ = 10.0, 2.0 Hz), and 5.82 (1 H, d of t, $J$ = 10.0, 3.0 Hz).

**C. Reductive Methylation of *p*-Methoxyacetophenone** (**6c**).—The product of reductive methylation of *p*-methoxyacetophenone (**6c**) showed two peaks other than those of the starting material in glpc carried out at 180°. One was identified as compound **1** and the other as an authentic sample of ***p*-methoxy-1-phenethyl**

(27) Predominant methylation at the oxygen atom of sodium acetylacetonate and potassium enolate of ethyl acetoacetate by a similar procedure has been reported. See A. L. Kurts, N. K. Genkina, A. Macias, I. P. Beletskaya, and O. A. Reutov, *Tetrahedron*, **27**, 4777 (1971).

(28) J. F. Eastham and D. R. Larkin, *J. Amer. Chem. Soc.*, **81**, 3652 (1959).

(29) H. L. Dryden, Jr., G. M. Webber, R. R. Burtner, and J. A. Cella, *J. Org. Chem.*, **30**, 3985 (1965).

(30) D. J. Cram and K. R. Kopecky, *J. Amer. Chem. Soc.*, **81**, 2748 (1959).

(31) Bands at 1335, 1129, and 1111 cm⁻¹ characteristic of the meso modification[30] were scarcely observable in the ir spectrum of the crude crystalline mass of the pinacol dissolved in $CCl_4$.

alcohol (**8a**), which was prepared by lithium aluminum hydride reduction of **6c**. The results of quantative analysis by glpc are shown in Table II. The nmr spectrum of the crude product also supported the above-described characterization.

**D. Reductive Methylation of *p*-Methylacetophenone (6d).**—The crude product obtained by reductive methylation of *p*-methylacetophenone (**6d**) in the same way as in A was chromatographed on silica gel thick layer plates. Elution with a 4:1 mixture of benzene–ethyl acetate yielded two fractions. The upper fraction was purified by bulb-to-bulb distillation to give a 1:1 mixture of cis and trans isomers of **1-acetyl-1,4-dimethylcyclohexa-2,5-diene (7c)**. On the basis of 100 MHz nmr spectrum, the product was concluded to be a 1:1 mixture of geometric isomers. *Anal.* Calcd for $C_{10}H_{14}O$: C, 79.95; H, 9.39. Found: C, 79.68; H, 9.26. Ir $\nu$ 1713, 1673, and 1628 $cm^{-1}$; mass spectrum *m/e* (rel intensity) 150 ($M^+$, 0.4), 107 (100), and 91 (96); nmr (100 MHz) $\delta$ 1.12 and 1.13 (3 H, two doublets, $J$ = 7.0 Hz), 1.18 and 1.19 (3 H, two singlets), 2.18 (1 H, m), 5.48 (2 H, overlapped d of d, $J$ = 10.0, 2.5 Hz), and 5.76 (2 H, overlapped d of d, $J$ = 10.0, 3.5 Hz). The lower fraction was shown to be *p*-methyl-1-phenethyl alcohol (**8b**) by comparison with an authentic sample, bp 73° (3 mm), prepared by lithium aluminum hydride reduction of **7c**. Quantitative analysis of the crude product was performed by employing phenylcyclohexane as internal standard at 160° and the result is shown in Table II.

**E. Reductive Methylation of 1-Tetralone.**—The reductive methylation of 1-tetralone was carried out in a way similar to A and the resulting product was chromatographed on silica gel. Continuous elution with benzene yielded successively 4% of tetralin and 60% of **8a-methyl-1,2,3,4,6,8a-hexahydronaphthalen-1-one (9)**. Distillation afforded an analytical sample, bp 62–63° (0.53 mm), $n^{22.5}D$ 1.5207. *Anal.* Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.39; H, 8.65. Ir $\nu$ 1708, 1688, and 1644 $cm^{-1}$; mass spectrum *m/e* (rel intensity) 162 ($M^+$, 10.3), 105 (65), and 91 (100); nmr $\delta$ 1.35 (3 H, s), 1.65–3.00 (8 H, m), 5.55 (1 H, m), 5.71 (1 H, d of t of d, $J$ = 10.2, 2.6, 1.8 Hz), and 5.97 (1 H, d of t, $J$ = 10.2, 1.5 Hz). 1-Tetralone (13%) was eluted last.

**Reductive Alkylation of Acetophenone. General Procedure.**—The method described for the reductive methylation of acetophenone was applied to the preparation of the lithium trienolate **4b**. A solution of 10.000 g (83.1 mmol) of acetophenone and 9.40 ml (1.2 × 83.1 mmol) of dry *tert*-butyl alcohol diluted with 40 ml of THF was introduced to 270 ml of redistilled ammonia.[29] To the stirred solution 7.15 g (2.2 × 83.1 mg-atoms) of small pieces of potassium was added quickly and the resulting solution was stirred at −78° under nitrogen for 10 min. Anhydrous lithium bromide (15.90 g, 2.2 × 83.1 mmol) was introduced into the resulting blue solution and stirring was continued for 1 hr. Removal of the ammonia afforded a viscous mixture, which was mixed with an alkylating reagent (2.0–2.2 × 83.1 mmol). When the reaction was too vigorous, the reagent was added in the form of a THF solution (ethyl bromoacetate). The resulting mixture was stirred at 0–10° for 20–40 min and the reaction mixture was worked up as was done for methylation. The crude product was either purified by fractional distillation (allyl bromide) or analyzed quantitatively by glpc (ethyl iodide, ethyl bromoacetate, and chloroacetonitrile) employing a pure sample obtained by separation using thick layer chromatography (silica gel). Results are listed in Table III.

**A. With Ethyl Iodide. 1-Acetyl-1-ethylcyclohexa-2,5-diene (10a)** had bp 73° (11 mm), $n^{25}D$ 1.4809. *Anal.* Calcd for $C_{10}H_{14}O$: C, 79.95; H, 9.39. Found: C, 79.65; H, 9.31. Ir $\nu$ 1704, 1673, 1630, and 1601 $cm^{-1}$; mass spectrum *m/e* (rel intensity) 151 (0.3), 150 ($M^+$, 0.3), and 79 (100); nmr $\delta$ 0.77 (3 H, t, $J$ = 7.5 Hz), 1.63 (2 H, q, $J$ = 7.5 Hz), 2.12 (3 H, s), 2.72 (2 H, m), 5.49 (2 H, d of t, $J$ = 7.5 Hz), and 5.95 (2 H, d of t, $J$ = 10.8, 3.0 Hz).

**B. With Allyl Bromide. 1-Acetyl-1-allylcyclohexa-2,5-diene (10b)** had bp 53–56° (0.8 mm), $n^{25}D$ 1.4950, $d^{25}25$ 0.9630. *Anal.* Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.74; H, 8.84. Ir $\nu$ 1705, 1675, 1638, and 919 $cm^{-1}$; mass spectrum *m/e* (rel intensity) 162 ($M^+$, 8) and 43 (100); nmr $\delta$ 2.10 (3 H, 2), 2.38 (2 H, m), 2.72 (2 H, m), 4.86, 5.06 (3 H, m), 5.51 (2 H, d of t, $J$ = 10.5, 2.0 Hz), and 5.91 (2 H, d of t, $J$ = 10.5, 3.0 Hz.

**C. With Ethyl Bromoacetate. Ethyl 1-acetylcyclohexa-2,5-dienylacetate (10c)** had bp 104° (0.9 mm), $n^{25}D$ 1.4822, $d^{25}25$ 1.0686. *Anal.* Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.51; H, 7.93. Ir $\nu$ 1726, 1710, 1674, and 1632 $cm^{-1}$; mass spectrum *m/e* (rel intensity) 210 (0.2), 208 ($M^+$, 0.2), and 91 (100); nmr $\delta$ 1.22 (3 H, t, $J$ = 7.0 Hz), 2.17 (3 H, s), 2.69 (2H, s), 2.76 (2 H, m), 4.10 (2 H, q, $J$ = 7.0 Hz), 5.70 (2 H, d of t, $J$ = 10.5, 1.3 Hz), and 5.95 (2 H, d of t, $J$ = 10.5, 3.0 Hz).

**1-Acetylcyclohexa-2,5-dienylacetic Acid (10d).**—This was obtained as a nonvolatile fraction, crystallized from ether–*n*-pentane, mp 96–98°, and identified with the authentic sample described below. *Anal.* Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.39; H, 6.68. Ir $\nu$ (KBr) 2740, 2660, 1717, 1708, 1673, and 1630 $cm^{-1}$; mass spectrum *m/e* (rel intensity) 181 (0.3), 180 ($M^+$, 0.2), 92 (100), and 91 (53); nmr $\delta$ 2.16 (3 H, s), 2.75 (4 H, m), 5.70 (2 H, d of t, $J$ = 10.3, 1.6 Hz), 5.97 (2 H, d of t, $J$ = 10.3, 3.0 Hz), and 8.51 (1 H, br). An authentic sample was obtained by refluxing a mixture of the ester **10c**, 2 *N* sodium carbonate, and methanol under nitrogen for 1 hr. Crystallization from ether–*n*-pentane produced the acid **10d**, mp 96–98°.

**With Chloroacetonitrile. 1-Acetylcyclohexa-2,5-dienylacetonitrile (10e).**—*Anal.* Calcd for $C_{10}H_{11}ON$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.35; H, 6.83; N, 8.79. Ir $\nu$ 2250, 1711, 1677, and 1633 $cm^{-1}$; mass spectrum *m/e* (rel intensity) 161 ($M^+$, 0.5), 91 (89), and 43 (110); nmr $\delta$ 2.17 (3 H, s), 2.65 (2 H, s), 2.89 (2 H, m), 5.54 (2 H, d of t, $J$ = 10.3, 2.0 Hz), and 6.17 (2 H, d of t, $J$ = 10.3, 3.2 Hz).

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**Registry No.**—**1**, 41477-77-4; **2**, 41477-78-5; **3**, 22985-90-6; **6a**, 579-74-8; **6b**, 586-37-8; **6c**, 100-06-1; **6d**, 122-00-9; **7a**, 41477-79-6; **7b**, 41477-80-9; *cis*-**7c**, 41477-81-0; *trans*-**7c**, 41477-82-1; **8a**, 3319-15-1; **8b**, 536-50-5; **9**, 41477-84-3; **10a**, 41477-85-4; **10b**, 41477-86-5; **10c**, 41477-87-6; **10d**, 41477-88-7; **10e**, 41477-89-8; acetophenone, 98-86-2.