3 H, ArOCH₃), 7.16-7.20 (m, 2 H, H₂,5), 7.35-7.39 (dd, 1 H, H₂,6, 7.5-7.6 (d, 1 H, H₂,6, 7.6-7.7 (d, 1 H, H₂,5), 7.98-8.03 (d, 1 H, H₂,6, 8.64-8.68 (d, 1 H, H₂,5), mass spectrum 458 (M⁺), 445, 415, 399, 367, 91; exact mass (EI⁺) caleld for C₉H₈N₂O₂ 416.2464, found 416.2461.

**Synthesis of Acetates 24a.** Reaction of distilled lepidine with alkyl 5b under similar conditions used to synthesize alcohols 23b gave the corresponding des-6-methoxy alcohol. These alcohols (23b) were not purified, but rather acetylated, directly to the corresponding des-6-methoxy acetates; 'H NMR (ppm, acetates) 1.93, 1.99 (s, 3 H, OCOCH₃), 2.04, 2.08 (s, 3 H, ArOCH₃), 4.26-4.46, 4.98-5.06 (m, 2 H, H⁻), 5.29-5.36 (m, 1 H, H⁺), 7.21-7.27 (m, 6 H, Ph, H₆), 7.59-7.63 (t, 1 H, H₇), 7.69-7.74 (t, 1 H, H₇), 8.11-8.23 (m, 2 H, H₆), 8.51-8.62 (d, 1 H, H₅).

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**Registry No.** (+)-5a, 134261-48-6; (+)-5b, 134261-60-2; 11, 134261-49-7; 12, 88946-48-9; 13a, 134261-50-0; 13b, 134261-59-9; 14, 134261-51-1; 16, 134261-52-2; (+)-17, 134261-53-3; (+)-18, 134261-54-4; (+)-19, 134261-55-5; (+)-20, 134261-56-6; (+)-23a (isomer 1), 134261-65-7; (+)-23a (isomer 2), 134261-66-8; (+)-23b (isomer 1), 134261-57-7; (+)-23b (isomer 2), 134261-61-3; (+)-24a (isomer 1), 134261-58-8; (+)-24a (isomer 2), 134261-64-8; (+)-24b (isomer 1), 134261-62-4; (+)-24b (isomer 2), 134261-63-5; Ph₂=P=CCOCH₃, 1439-36-7; CH₂COC=CH₂, 78-94-4; 6-methoxy-4-methylquinoline, 41037-26-7; 4-methoxyaniline, 104138-80-0; (+)-24b (isomer 2), 134261-63-5; Ph₂=P=CCOCH₃, 1439-36-7; CH₂COC=CH₂, 78-94-4; 6-methoxy-4-methylquinoline, 41037-26-7; 4-methoxyaniline, 104-94-9; lepidine, 491-55-0.

**Supplementary Material Available:** NMR spectra of each compound that appears in the Experimental Section and X-ray crystallography data for cis-18 (37 pages). Ordering information is given on any current masthead page.

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**Electronic and Steric Effects in the Addition of Electrophilic 1,3-Dicarbonylalkyl Radicals to Styrenes**

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The addition reactions of 1,3-dicarbonylalkyl radicals to ring-substituted styrenes have been kinetically investigated in MeOH and/or MeCN. It has been observed that the rate effect of ring substituents is nearly identical in the reactions of MeCOCHCOMe (1), MeCOCHCOMe (2) and MeOCOCHCOMe (4), the ρ value, in MeOH being -0.96, -1.01 and -1.06, respectively. Since the three radicals are relatively strong oxidants and have similar reduction potentials, Me > Et > Pr > Bu. The observed effects are much larger than those reported for the corresponding reactions of the nucleophilic cyclohexyl radical. It is suggested that the a-alkyl substituents exert an effect of steric inhibition of resonance thereby ring delocalization of the charge and/or unpaired electron in the transition state is significantly reduced. Delocalization may be more important in the reactions of 1 and 4 than in those of the cyclohexyl radical since it is possible that the former utilizes a transition state occurring later along the reaction coordinate and/or characterized by a larger extent of charge transfer.

In the last two decades, the addition reactions of carbon-centered radicals to alkenes have been intensively investigated both from the theoretical and the practical point of view. Most of the research has however been...
concentrated on the reactions of the nucleophilic alkyl radicals that are now known in satisfactory detail at least for what concerns the mechanistic aspects as well as the role of electronic and steric effects.\(^\text{1,2}\)

Thus, at present it is generally agreed that substituents in the alkene influence the rate mostly by polar effects, whereas the stability of the formed intermediate radical seems to be less important. Steric effects can also play a significant role, but only when the substituent is at the position of the alkene attacked by the nucleophilic radical. Substituents in the attacking radical can influence the reactivity by steric and polar effects. Very interestingly, electron-donating groups increase the nucleophilic character of the radical and make it more reactive as well as more selective.

The extension of the previous conclusions to the addition reactions of electrophilic carbon-centered radicals is not, however, straightforward. The SOMO orbital of the radical should now interact with the HOMO orbital of the alkene and not with the LUMO as it occurs in the reactions of nucleophilic radicals.\(^\text{6}\) Moreover, electrophilic carbon-centered radicals are generally significantly more stable than alkyl radicals, and this might lead to a transition-state structure more shifted toward that of the products.

Thus, differences in the behaviors of nucleophilic and electrophilic radicals can certainly be envisaged, and in fact, it has recently been observed that these radicals behave differently in the regiochemistry of the ring-closure reactions of 5-hexenyl radicals.\(^\text{9}\)

In spite of these points of interest, mechanistic studies concerning the addition reactions of electrophilic carbon-centered free radicals have so far received little attention, even though there are signs that the situation is changing,\(^\text{10-15}\) probably on the wake of the relevant number of works that in the last few years have concerned the synthetic exploitation of the oxidative addition of carbonyl compounds to alkenes, a reaction involving the intermediacy of electrophilic radicals.\(^\text{6}\)

In collaboration with Giese and Farshchi, we have recently carried out a kinetic study of the addition reactions of malonyl radicals to substituted styrenes. Malonyl radicals were generated both oxidatively, by reaction of cerium(IV) ammonium nitrate (CAN) with a dialkyl malonate, and reductively, by reaction of a dialkyl chloromalonate with tributyltin hydride. Interestingly, the reaction selectivity of the addition process turned out to be the same, under the two experimental conditions, thus suggesting that also in the CAN-promoted additions the generated malonyl radical is a free species not significantly complexed to the metal.

Having clarified this point, we have continued our study with the 2-fold aim of determining the influence of the structure of the radical on the reaction selectivity and of getting information on the sensitivity of the reaction to steric effects. Thus, in this paper we report on a kinetic investigation concerning the reactions of \(a,\alpha\)-dicarbonylalkyl radicals \(\text{MeCOCHCOMe} (1)\) and \(\text{MeCOCHCOMe} (2)\) with the ring \(Z\)-substituted styrenes 3a–3e \((a, Z = H;\)


\(^{(8)}\) However, it has been suggested that the SOMO–HOMO interaction is the dominant one also with nucleophilic radicals.\(^\text{46}\)


\(^{(14)}\) Reference 12 and references cited therein.


might C. the alkyl nitrate. process that makes the addition reaction irreversible. It has also been checked that changing the CAN concentration (up to a factor of 3) has no effect on the reactivity ratio values, which indicates that the formation of the dihydrofuran group, served in the addition of malonyl radicals to the styrenes.15 3a-5d the methoxy addition products 3a-5d have been generated by reaction of CAN with 2,4-pentanedione, methyl 3-oxo-butyrate (both in MeCN and MeOH) with the alkenes 5a-5d. The radicals 1, 2, and 4 have been generated by the methoxy addition products 3a-5d. The radicals 1, 2, and 4 have been generated by reaction of CAN with 2,4-pentanedione, methyl 3-oxo-butyrate, and dimethyl malonate, respectively.

Results and Discussion
The CAN-induced oxidative addition of carbonyl compounds to styrenes is illustrated in Scheme I. The key intermediate is the radical 6, which undergoes an oxidative ligand transfer to give the alkyl nitrate 7. From 7 the final products are obtained by intramolecular nucleophilic displacement of the nitrate group and/or solvolytic reactions.16,17,18 The reactions of 2,4-pentanedione and methyl 3-oxo-butyrate (both in MeCN and MeOH) with the alkenes 3a-3e and of 2,4-pentanedione with 5a-5d always led to the formation of the dihydrofuran 8, as expected on the basis of previous works concerning the oxidative addition of 1,3-diketones and β-keto esters to alkenes.19-21 In all cases, the yields were very large: at least 80%, but generally much higher (see Experimental Section).

The CAN-promoted reactions of dimethyl malonate (4) take place with appreciable rate only in MeOH. With 5a-5d the methoxy addition products 9 were obtained together with substantial amounts of the lactone 10, the overall yield of the two products being ca. 90%.

![Figure 1. Hammett plot for the addition of 1 to ring-substituted styrenes in MeCN (β = -1.08; r = 0.998). Data from Table I.](image)

The relative rate constants of substituted styrenes with respect to styrene were determined by the competitive method. Two styrenes were reacted with 25-50% of the stoichiometric amounts of dicarbonyl compound and CAN and the moles of the two styrenes, before and after reaction, determined by GC. It has also been checked that changing the CAN concentration (up to a factor of 3) has no effect on the reactivity ratio values, which indicates that the trapping of the intermediate radical 6 by CAN is a fast process that makes the addition reaction irreversible.

For the reactions of 2,4-pentanedione, some competitive experiments were also carried out by using a large excess of the two styrenes and determining the relative amount of the two reaction products. An excellent agreement was observed with the results obtained with the previous method. All kinetic results are collected in Tables I-III.

### Electronic Effects
The effect of the ring substituents on the rate of addition of the radicals 1 and 2 to styrenes is displayed in Table I and II, respectively. The reactions of the two radicals exhibit substituent effects that are very similar and also are almost independent of the solvent used (MeOH and MeCN). Nearly identical values can therefore be calculated from the very good linear correlations between the logs of the relative reactivities and the σ+ values of the ring substituents: -1.08 (MeCN) and -0.96 (MeOH) for 1; -0.99 (MeCN) and -1.01 (MeOH) for 2.

If we now also consider that the reaction constant for the addition reactions of malonyl radical to ring-substituted styrenes is -1.06 in MeOH, we come to the obvious conclusion that the selectivity of the addition of α-oxoalkyl radicals to styrenes is not significantly influenced by the radical structure as well as by the nature of the solvent. The former conclusion is quite surprising since the stability of the radical is expected to decrease in a substantial way.
in the order $1 > 2 > 4$, and the same order should hold for the electrophilic character. Thus, by analogy with the properties of nucleophilic radicals, the prediction was that as we progressively replace the acetyl groups by the carboalkoxy groups the reaction selectivity of the radical should decrease, which is contrary to the observations.

It has, however, to be noted that radicals 1, 2, and 4 are relatively strong oxidants with very similar reduction potentials (between 0.73 and 0.75 V vs NHE in DMSO). Thus, the insensitivity of the reaction selectivity to the radical stability might be explained on the basis of an important contribution of structures like 11, where a substantial charge transfer from the alkene to the radical has taken place, to the transition state of the reaction.

$[(RCO)_{2}CH]-[CH_{2}CH_{2}CH}H_{2}]^{+}$

In this situation, the selectivity of the addition process would mostly be influenced by the ability of the radical to accept a negative charge; an ability that, on the basis of the reduction potential values, appears to be very similar for the three radicals under study.

We have tried to test this hypothesis by determining the relative reactivity for the couple $p$-methylstyrene and styrene in the reaction with 1 in MeCN, in the presence of LiClO$_{4}$. We felt that an increase of the $p$-methylstyrene to styrene reactivity ratio might be observed under these conditions, since it has recently been reported that the oxidizing power of 1 in DMSO significantly increases in the presence of LiClO$_{4}$ (the reduction potential becomes 0.5 V more positive), probably owing to the ability of Li$^{+}$ to coordinate the anion. However, as shown in Table 1, we found that the presence of LiClO$_{4}$ up to 0.6 M has practically no significant effect on the value of the $p$-methylstyrene to styrene reactivity ratio.

In spite of this negative result, we feel that the earlier suggestion still deserves further consideration since it cannot be excluded that the buildup of negative charge on the oxygen atoms in the transition state has not yet become big enough to produce a significant interaction with Li$^{+}$ ions. Moreover, in MeCN (the solvent for our reactions) LiClO$_{4}$ is certainly more strongly associated than in DMSO, and Li$^{+}$ may therefore be less available for coordination. Additional experimentation is necessary to clarify this interesting point.

As already mentioned, previous work has provided results indicating that, in the CAN-promoted additions of the malonyl radical, coordination of the radical with cerium ions is insignificant. It seems safe to extend this conclusion also to the reactions of 1 and 2 in view of the very similar behaviors of these radicals with respect to those of the malonyl radical.

**Steric Effects.** In Table III the relative reactivity data concerning the reactions of $\alpha$-alkyl-substituted styrenes 5a–5d with 1 and 4 are reported. It can be immediately seen that the rate of both reactions is significantly influenced by the nature of the $\alpha$-alkyl group, the effects being slightly larger in the former. No significant solvent effect (MeOH vs MeCN) has been observed.

With respect to the unsubstituted styrene, the presence of an $\alpha$-methyl group increases the reaction rate, as expected for an electrophilic process favored by electron-releasing groups. The effect is, however, relatively small (it is not much different from that of a ring $p$-methyl group), which suggests the presence of a significant rate-retarding steric effect. This is confirmed by the observation of a progressive decrease of the addition rate as we increase the steric requirements of the alkyl group, moving from methyl to ethyl, isopropyl, and tert-butyl.

Since we can reasonably assume a very similar electronic effect for the previous alkyl groups, the observed decrease in the relative reactivity values can quite confidently be attributed, at least for the most part, to the operation of steric effects. Accordingly, a plot of the logs of the relative reactivities against the steric substituent constants $E_{4}$ of the alkyl groups exhibits an excellent linearity for the two reactions (Figure 2) with a $\rho$ value of 1.73 for the reaction of 1 and of 1.22 for the reaction of 4.

In Figure 2 some very recent data concerning the additions of dicyanomethyl radical to the same substrates are also plotted. It is remarkable to note that this reaction exhibits a sensitivity to steric effects very similar to that shown by the reaction of 1, in spite of the fact that the steric demand of the latter radical is significantly larger than that of the former. Another very intriguing observation is that the sensitivity to steric effects exhibited by the reactions of 1 and 4 as well as by that of the cyanoalkyl radical with $\alpha$-substituted styrenes is enormously higher than that found in the corresponding reactions of the cyclohexyl radical. Thus, the $\alpha$-methyl/ $\alpha$-tert-butyl ratio is ca. 300 in the reaction of 1 in MeOH and only 1.6 in the reaction of cyclohexyl radical!

The reasons of this dramatic difference are not clear, since we certainly cannot think of a very large difference in bulkiness of the cyclohexyl radical with respect to 1 and 4 and, moreover, we have already observed that the steric demand of the attacking radical does not play a significant role with regard to the effect of the $\alpha$-alkyl substituents on the rate of addition to styrenes.

Since the steric requirements of the radical seem to be of secondary importance, a more significant role could be played by the character (electrophilic vs nucleophilic) of

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(25) Zippe, H.; He, J.; Giese, B.; Houk, K. N. Submitted for publication. The relative rates for the alkyl groups are MeEtPr = 1:0.43±0.14. Private communication by Prof. Giese.
the radical. Accordingly, the available data seem to indicate that the sensitivity to the effects of α-substituents in the styrene moiety increases as we move from nucleophilic to electrophilic to carbonyl-centered radicals. This is nicely confirmed by recent results concerning the cyano-methyl radical, a borderline radical between electrophilic and nucleophilic behaviors. In the reaction of full-fledged electrophilic radicals like methyl radical, a borderline radical between electrophilic to nucleophilic behaviors, I2 in the reaction of α-alkyl radicals occurs later along the reaction coordinate than that for the addition of an alkyl radical, since the former are significantly more stable than the second. If this suggestion, which is in accord with ab initio calculations of Giese and associates, is correct, the delocalization, in the transition state, of the developing charge and/or unpaired electron should play a much more important role in the reactions of electrophilic carbonyl- and cyano-substituted radicals than in those of nucleophilic alkyl radicals. As a matter of fact, in the case of the radicals 1 and 4 the importance of this delocalization is also suggested by the substantial effects of ring substituents on the addition rate. Of course, such a delocalization requires that the phenyl ring keeps coplanar with the double bond. A consequence is that as the steric requirements of the α-alkyl group increase, the extent of charge delocalization in the ring can significantly be reduced since the phenyl group experiences increasing difficulty to align its π system with that of the double bond (steric inhibition of resonance).

This effect might be much less important in the addition reactions of nucleophilic alkyl radicals to styrenes because these reactions should utilize a very early transition state where, as already suggested, charge delocalization in the phenyl ring is of little importance. That this is the case, at least with the cyclohexyl radical, is clearly indicated by the observation of Giese and co-workers that the addition of this radical to 12 is only 3.9 times faster than to 13 in spite of the fact that charge delocalization is much more efficient in the former alkenes where the two aromatic rings are forced to be coplanar with the double bond by the bridging methylene group.

**Experimental Section**

1H NMR spectra were recorded at 80 MHz on a Bruker SY 80 and, when specified, at 200 MHz on a Bruker AC 200 spectrometer in CDCl₃ solution and in the presence of tetramethylsilane as an internal standard. IR spectra were registered on a Perkin-Elmer M-297 spectrophotometer. Mass spectra were recorded on a Hewlett-Packard 5980-5970 combined GC-MS at 70 eV. Elemental analyses were performed on a Carlo Erba M 1106 elemental analyzer. Melting points were determined with a Buchi M 510 instrument and were uncorrected. Gas chromatographic analyses were performed on a Hewlett-Packard 5880 A instrument (30 m, SP-B5, capillary column).

Starting Materials. Acetonitrile, methanol, 2,4-pentanediene, methyl 3-oxobutanoate, and dimethyl malonate, of the highest grade of purity (Aldrich), were used without further purification. Purified unsubstituted styrene and p-methyl-, p-chloro-, and p-methoxystyrenes were obtained from 29 α-Methylstyrene (Fluka) was fractionally distilled before use; 2-phenyl-1-butene, 3-methyl-2-phenyl-1-butene, and 3,3-dimethyl-2-phenyl-1-butene were prepared by the Wittig reaction from ethyl, isopropyl, and tert-butyl phenyl ketone, respectively, and methylnitrophenylphosphorane according to the following standard procedure: to a solution of disopropylamine (7.7 g, 76 mmol) in 100 mL of anhydrous tetrahydrofuran cooled at −60 °C was added n-butyl lithium (0.1 M in hexane, 76 mL) dropwise under nitrogen. After 15 min, methylnitrophenylphosphorane iodide (30.7 g, 76 mmol) was added under stirring. The cold bath was removed, and the mixture was allowed to react 2 h at room temperature. The mixture was added dropwise to the mixture was allowed to react for a period of time ranging from 1 to 10 h depending on the structure of the ketone. After filtration and solvent evaporation, light petroleum was added and most of the crystallized triphenylphosphine oxide was removed by filtration. Chromatographic of the resulting solution on silica gel (light petroleum as the eluent) and successive distillation give α-alicyl-substituted styrene more than 99.9% pure by GLC analysis. 2-Phenyl-1-butene (5b): 68%; bP 64-64.5 °C; 1H NMR δ 7.50-7.75 (m, 4 H), 5.28 (m, 1 H), 5.07 (m, 1 H), 4.20 (m, 2 H), 2.52 (m, 2 H), 2.10 (m, 2 H), 1.10 (m, 1 H), 0.85 (m, 1 H); MS m/z 132 (M⁺, 67), 117 (100), 103 (93), 77 (33), 53 (18). 3-Methyl-2-phenyl-1-butene (5e): 71%; 1H NMR δ 7.35-7.19 (m, 5 H), 5.13 (dd, J = 0.6 and 1.4 Hz, 1 H), 5.03 (t, J = 1.7 Hz, 1 H), 2.84 (b sept, J = 6.9 Hz, 1 H), 1.11 (d, J = 6.9, 6 H); MS m/z 146 (M⁺, 37), 131 (100), 115 (13), 103 (30), 91 (42), 77 (26). 3,3-Dimethyl-2-phenyl-1-butene (5d): 51%; bP 76-77 °C; 1H NMR δ 7.32-7.20 (m, 3 H), 7.17-7.10 (m, 2 H), 5.17 (d, J = 1.7 Hz, 1 H), 4.76 (d, J = 1.7 Hz, 1 H), 1.11 (s, 9 H); MS m/z 160 (M⁺, 38), 145 (100), 104 (67), 91 (34), 77 (31), 57 (39).

Structure Determination of the Reaction Products. To a solution of CAN (50.0 g, 311 mmol) in 50 mL of solvent were added unsubstituted styrene (20 mmol) and dicarbonyl compound (4.5 mmol) in 10 mL of the same solvent at 20 °C, and the mixture was allowed to react until CAN was completely reduced (5 min in the reaction with 2,4-pentanediene and methyl 3-oxobutanoate, 40 min in the reaction of dimethyl malonate, after iodometric titration). The mixture was poured into water (250 mL) and extracted with diethyl ether (8 × 100 mL); the collected extracts were washed with water (200 mL) and dried with sodium sulfate, and the solvent was evaporated under vacuum (15 mmHg). Chromatographic of the residue on silica gel after elution with 8:2 petroleum ether-diethyl ether mixture allowed the isolation of the reaction products that were characterized as follows.

**Reaction with 2,4-Pentanediene.** 3-Acetyl-2-methyl-5-phenyl-4,5-dihydrofuran [8 (R = R′ = Me, Ar = C₆H₅); 91% ; 1H NMR δ 7.35 (s, 5 H), 5.10 (4 peaks, X portion of an ABX system, 1 H), 3.57-2.82 (eight quarts, 2.82) 1.4 Hz, J = 1.4 Hz, AB portion of an ABX system, 2 H), 2.31 (t, J = 1.4 Hz, 3 H), 2.21 (s, 3 H); IR (film) 3030-3000, 2920, 2860, 1671, 1620, 1605, 1495, 932, 760 cm⁻¹; MS m/z 202 (M⁺, 40), 183 (13), 159 (10), 115 (26), 91 (10), 77 (11), 43 (100). Anal. Calc. for C₁₃H₁₂O₂: C, 77.20; H, 6.98. Found: C, 77.02; H, 7.04. 3-Acetyl-2-methyl-5-p-tolyl-4,5-dihydrofuran [8 (R = R′ = Me, Ar = p-Me₃C₆H₄); 89%; 1H NMR δ 7.21 (s, 4 H), 5.57 (4 peaks, X portion of an ABX system, 1 H), 3.53-2.80 (eight quarts, 2.80) 1.4 Hz, J = 1.4 Hz, AB portion of an ABX system, 2 H), 2.30 (s, 3 H), 2.30 (t, J = 1.4 Hz, 3 H), 2.20 (s, 3 H); IR (film) 3012, 2920-2860, 1670, 1596, 1515, 1225, 932, 817 cm⁻¹; MS m/z 216 (M⁺, 22), 183 (9), 155 (7), 115 (9), 91 (8), 77 (5), 43 (100). Anal. Calc. for C₁₃H₁₁O₂C: 77.75; H, 7.46. Found: C, 77.61; H, 7.39. 3-Acetyl-2-methyl-4-(chlorophenyl)-4,5-dihydrofuran [8 (R = R′ = Me, Ar = p-CIC₆H₄); 67%; 1H NMR δ 7.40-7.18 (m, 4 H), 5.57 (4 peaks, X portion of an ABX system, 1 H), 3.57-2.77 (eight quarts, 2.77) 1.4 Hz, AB portion of an ABX system, 2 H), 2.31 (t, J = 1.4 Hz, 3 H), 2.22 (s, 3 H); IR (film) 3025, 3015, 2920, 2860, 1672, 1620, 1605, 1492, 1228, 932, 828, 89 cm⁻¹; MS m/z 236

(26) In ref 25, ab initio calculations have indicated a somewhat later transition state for the reaction of malononitrile radical with ethylene compared to that of addition of methyl radical.

(27) tert-Butyl phenyl ketone was obtained in 95% yield by reaction of lithium diphenylcuprate with pivaloyl chloride in THF at −60 °C.
3-Acetyl-2-methyl-5-(m-nitrophenyl)-4,5-dihydrofuran [8 (R = R' = Me, R" = H, Ar = c-C6H4Cl): 88%; H NMR 7.37 (m, 5 H), 2.97 (s, 3 H), 2.95 (d, J = 1.8 Hz, 3 H), 2.19 (sept, J = 6.5 Hz, 1 H), 0.93 (d, J = 6.5 Hz, 6 H); IR (film) 3095-3005, 2970-2880, 1755, 1735, 1602, 1386, 1260, 748, 705 cm−1; MS m/z 265 (M+ − 68), 233 (5), 205 (44), 140 (1), 77 (27), 43 (36). Anal. Calcd for C16H14O2: C, 66.21; H, 7.84. Found: C, 66.02; H, 7.87. Moreover, a viscous colorless oil was recovered whose H NMR, IR, and C, H analysis were consistent with a 2:1 mixture of disastereoisomeric 5-propenyl-2-methyl-4,5-dihydrofurancarbonyl-butan-2-ene-1-carboxylic acids [10 (R = OMe, R' = Me, R" = c-C6H4Cl): 42%]. H NMR referred to the main isomer δ 7.36 (s, 5 H), 3.79 (s, 3 H), 3.3 (m, 1 H), 2.91 (t, J = 6.5 Hz, 2 H), 2.19 (septet, J = 6.5 Hz, 1 H), 0.91 (d, J = 6.5 Hz, 6 H); IR of the mixture (film) 3095–3005, 2970, 2870, 1740, 1685, 1450, 1210, 1100, 705 cm−1. Anal. Calcd for C16H18O2: C, 68.68; H, 6.92. Found: C, 68.67; H, 7.05. After hydrolysis by reflux of the mixture with alcoholic potassium hydroxide for 1 h then acidification and decarboxylation at 180°C, a single product was obtained after chromatography on silica gel (1:1 petroleum ether–diethyl ether mixture, allowed the isolation of the following products. 5a gave methyl 2-(methoxycarbonyl)-4-methoxy-5-phenyl-4-phenoxyhexanoate [9 (R = R' = OMe, R" = Pr, Ar = C6H4Br): 48% yield: δ H NMR 7.3 (m, 5 H), 3.74 (s, 3 H), 3.57 (s, 3 H), 3.49 (three peaks, X portion of an AB system, 1 H), 3.18 (s, 3 H), 2.89–2.67 (seven peaks, AB portion of an AB system, 2 H), 2.06 (s, 2 H); IR (film) 3095–3005, 2980–2850, 1747, 1735, 1608, 1084, 765, 705 cm−1; MS m/z 265 (M+ − 68), 233 (5), 205 (44), 140 (1), 77 (27), 43 (36). Anal. Calcd for C16H16O4: C, 66.21; H, 7.84. Found: C, 66.02; H, 7.87.
Stereochemical Control of Microbial Reduction. 17. A Method for Controlling the Enantioselectivity of Reductions with Bakers' Yeast

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The stereoselectivity of the bakers' yeast catalyzed reduction of β-keto esters to optically active β-hydroxy esters can be controlled by the introduction of a third reagent. To gain insight into the mechanism of this enzymatic reduction, β-hydroxy ester oxidoreductases were isolated from the cells of raw bakers' yeast. Four dominant competing enzymes were isolated, purified, and characterized. Among these, two reduce β-keto esters stereospecifically to the corresponding D-β-hydroxy esters. The other two afford the L-hydroxy esters. The rates of enzymatic reduction were determined in the presence and absence of the additives.

Introduction

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Stereochemical Control of Microbial Reduction. 17. A Method for Controlling the Enantioselectivity of Reductions with Bakers' Yeast

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The stereoselectivity of the bakers' yeast catalyzed reduction of β-keto esters to optically active β-hydroxy esters can be controlled by the introduction of a third reagent. To gain insight into the mechanism of this enzymatic reduction, β-hydroxy ester oxidoreductases were isolated from the cells of raw bakers' yeast. Four dominant competing enzymes were isolated, purified, and characterized. Among these, two reduce β-keto esters stereospecifically to the corresponding D-β-hydroxy esters. The other two afford the L-hydroxy esters. The rates of enzymatic reduction were determined in the presence and absence of the additives.

Introduction

The development of methods for the synthesis of optically active compounds has become one of the most important goals in the fields of organic chemistry and biochemistry. In recent years, there have been dramatic developments in the asymmetric synthesis of organic compounds. In particular, biological methods have been extensively developed within the last decade.

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