independent Friedel pairs, alternately collected in the range $2° < \theta < 65°$ on a computer-controlled four-circle diffractometer. Some experimental details are the following: $\omega/2\theta$ scan mode; 1.40° scan width; 0.035° sg^{-1} scan speed with the same measurement time for both backgrounds as for the peak. Graphite-monochromated Cu Kα radiation (1.5418 Å) was used. No crystal decomposition was observed during the data collection process. After the usual correction for Lorentz and polarization effects, 1742 Friedel pairs were considered as observed according to the criterion $I > 2\sigma(I)$ and were used in the least-squares refinement.[16] No absorption correction was applied. The atomic scattering factors and the anomalous dispersion corrections were taken from the literature.[17] The structure was solved by direct methods.[18] The hydrogen atoms were placed at their expected positions, but they were checked in a Fourier difference map and included as fixed contributors in the refinement. For the last refinement Δ^2F was weighted with $w = w_1w_2$, where $w_1 = 1/(a + b|F_o|)^2$ and $w_2 = 1/(c + d(\sin\theta)/\lambda)$ with coefficients calculated in order to prevent bias in $w\Delta^2F$ vs. $|F_o|$ and $|(\sin\theta)/\lambda|$.[19] Several cycles of weighted anisotropic refinement including both hkl and $\bar{h}\bar{k}\bar{l}$ gave for the right enantiomer the following unweighted and weighted discrepancy indices: $R = 0.056$ and $R_w = 0.064$. The absolute configuration was confirmed by comparing the 72 more relevant Bijvoet pairs, giving the following discrepancy indices:[20] average Bijvoet difference $R_1 = \sum||F_o(+h) - F_o(-h)] - [F_c(+h) - F_c(-h)||/N = 0.603$ (0.666 for the reversal enantiomorph), average Bijvoet ratio $R_2 = \sum|R_o - R_c|/N = 0.072$ (0.076), and $R_3 = \sum|\Delta I_o - \Delta I_c|/\sum|\Delta I_o| = 0.901$ (1.113 for the reversal enantiomorph), with $N = 72$, $R_o = \Delta I_o/\langle F^2_o\rangle$, $R_c = \Delta I_c/\langle F^2_o\rangle$, $\Delta I_o = F^2_o(+h) - F^2_o(-h)$, and $\Delta I_c = F^2_c(+h) - F^2_c(-h)$.

Acknowledgment. We thank Dr. J. Borja, Botany Department, Faculty of Pharmacy, Madrid, for collection and botanical classification of the plant material and Professor S. García-Blanco for his support. We also thank the Centro de Proceso de Datos del Ministerio de Educación (Madrid) for the use of a 1108 UNIVAC computer. This work was supported in part by the National Research Council (CNR), Rome.

Registry No. 1, 77984-53-3; 2, 77984-54-4; 3, 77984-55-5.

Supplementary Material Available: A list of bond distances, bond angles, deviations of atoms from the ring planes, and torsion angles (6 pages). Ordering information is given on any current masthead page.

(16) Stewart, J. M.; Kundell, F. A.; Baldwin, J. C. "The X-Ray 70 System"; Computer Science Center, University of Maryland; College Park, MD, 1970.
(17) "International Tables for X-Ray Crystallography"; Kynoch Press: Birmingham, 1974; Vol. IV.
(18) Main, P.; Lessinger, L.; Woolfson, M. M.; Germain, G.; Declercq, J. P. "MULTAN"; Physics Department, University of York: England, 1977.
(19) Martínez-Ripoll, M.; Cano, F. H. "PESOS"; Instituto "Rocasolano", CSIC: Serrano 119, Madrid-6, Spain, 1975.
(20) Martínez-Ripoll, M.; Fayos, J. "CONFAB"; Instituto "Rocasolano", CSIC: Serrano 119, Madrid-6, Spain, 1977.

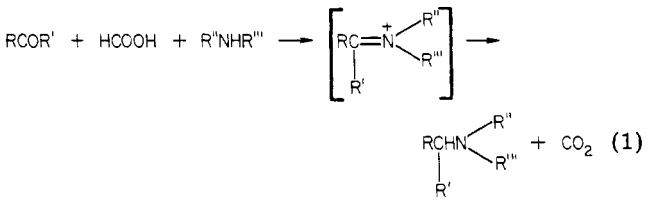
Reduction of Aldehydes and Ketones Using Sodium Formate in 1-Methyl-2-pyrrolidinone

James H. Babler* and Steven J. Sarussi

Department of Chemistry, Loyola University of Chicago, Chicago, Illinois 60626

Received January 13, 1981

Recently Heck and co-workers have reported[1] the reduction of alkynes, aromatic halides, conjugated dienes, and several other types of functionalized organic compounds using triethylammonium formate in the presence of a palladium catalyst. Prior to initiation of their studies, it was well-known that ammonium formate by itself was capable of reducing iminium salts to amines (the Leuckart reaction[2]). Subsequently Wallach[3] demonstrated that better results could be obtained in the latter reaction by using a mixture of ammonia or a substituted amine with formic acid (eq 1).



(1)

Although there is a legion of methods available for effecting the reduction of a carbonyl moiety to the corresponding alcohol,[4] formic acid (or formate salts) has not been utilized for this transformation. In a study involving the preparation of tertiary *N,N*-dimethylamines by the Leuckart reaction, Bach reported[5] that treatment of cyclooctanone with formic acid and *N,N*-dimethylformamide in an autoclave at 190 °C afforded, in addition to the expected tertiary amine, cyclooctanol as a byproduct in 10% yield. Intrigued by this report, we decided to investigate the potential use of formic acid in the reduction of aldehydes and ketones.

Results of our initial experiments using 4-phenyl-2-butanone as a representative substrate were discouraging. Treatment of this ketone with formic acid (2 molar equiv) in 1-methyl-2-pyrrolidinone at reflux afforded only a trace (<3%) of any reduction product after 18 h. In order to enhance the ability of formic acid to function as a hydride donor, triethylammonium formate was prepared[6] in situ by addition of a molar excess of triethylamine to the same reaction mixture. However, after 20 h at reflux, isolation of the reaction product and subsequent NMR and VPC analysis showed the presence of only 4% 4-phenyl-2-butanol, the rest of the material being starting ketone.

In view of the above results, we were pleasantly surprised by the fact that treatment of 4-phenyl-2-butanone with sodium formate (2.5 molar equiv) in 1-methyl-2-pyrrolidinone[7] containing 1 molar equiv of potassium phosphate monobasic as a buffer[8] afforded, after 20 h at reflux, 4-phenyl-2-butanol in 40% yield, contaminated only by the starting ketone. A similar experiment conducted

(1) Weir, J. R.; Patel, B. A.; Heck, R. F. *J. Org. Chem.* **1980**, *45*, 4926 and references therein.
(2) Leuckart, R. *Chem. Ber.* **1885**, *18*, 2341. Leuckart, R.; Bach, E. *Ibid.* **1886**, *19*, 2128. For a review of the Leuckart reaction, see: Moore, M. L. *Org. React.* **1949**, *5*, 301.
(3) Wallach, O. *Justus Liebigs Ann. Chem.* **1905**, *343*, 54.
(4) March, J. "Advanced Organic Chemistry: Reactions, Mechanisms, and Structure", 2nd ed.; McGraw-Hill: New York, 1977; pp 829-834.
(5) Bach, R. D. *J. Org. Chem.* **1968**, *33*, 1647.
(6) This experiment was run by refluxing a mixture of 3 mmol of 4-phenyl-2-butanone, 0.25 mL (6.64 mmol) of 98% formic acid, 1.2 mL (8.6 mmol) of triethylamine, and 4 mL of 1-methyl-2-pyrrolidinone for 20 h.
(7) Although use of other dipolar aprotic solvents that enhance the nucleophilicity of formate anion might be possible for this reaction, a mixture of 3:1 (v/v) *N,N*-dimethylformamide–hexamethylphosphoramide was clearly inferior and led (especially for the less easily reduced ketones) to a substantial amount of amine byproduct. Presumably a transformation similar to that reported by Bach[5] had occurred in the reaction mixture.
(8) No systematic study of the advantage of this or other buffers was attempted. However, replacement of monobasic potassium phosphate by an equivalent amount of boric acid led to poorer results (as evidenced by a significant increase in the formation of unidentified byproducts) in an experiment involving reduction of *p*-tolualdehyde.

0022-3263/81/1946-3367$01.25/0

Table I. Reduction[a] of Representative Aldehydes and Ketones

starting carbonyl compd[b]	reacn time, h	% yield (distilled product)	product[c] distribution,[d] % alcohol	starting material	all other components
p-tolualdehyde	21	65	>99[e]	0[f]	<1
decyl aldehyde	16	69	>95	0[f]	<5[g]
cinnamaldehyde	19	36[h]	>98[i]	0[f]	<2
4-phenyl-2-butanone	20	90	40	60	0
4-phenyl-2-butanone	43	91	64	36	0
propiophenone	45	90	53	47	0
2-methylcyclohexanone	45	76	94[j]	5	1

[a] All reactions were run for the specified time, using the general procedure listed in the Experimental Section. [b] Available from Aldrich Chemical Co., Milwaukee, WI. [c] The IR and NMR spectral properties of each alcohol product were identical with those exhibited by the authentic compounds sold by Aldrich Chemical Co. [d] These ratios were determined by VPC analysis (6 ft × 1/8 in. 2.5% Carbowax 20M column; retention times, alcohol > ketone). The percentages refer to peak areas without correction for response factors relative to an internal standard. The data obtained were fully consistent with the ratios of alcohol to starting material obtained by NMR analysis of the product mixture. [e] mp 57–58 °C (melting point of an authentic sample of *p*-tolylcarbinol 60 °C). [f] IR and NMR analysis indicated the absence of any unreduced aldehyde. [g] The rest of the product consisted of essentially one component, identified by spectral analysis as decyl formate: IR (film) ν_{max} 1725 (C=O), 1170 cm^{-1}; NMR (CCl_4) δ_{Me_4Si} 8.02 [s, HC(=O)OR], 4.13 (t, J = 6 Hz, CH_2O). [h] The yield of crude product was 90%; bp (of distillate) 45–75 °C (bath temperature, 0.07 mm). [i] NMR analysis indicated the alcohol product to be a 2:1 mixture of cinnamyl alcohol and 3-phenyl-1-propanol, respectively, the latter presumably arising from initial 1,4-reduction of the α,β-unsaturated aldehyde. Since the crude product consisted largely of dark-colored high-boiling material, the extent of conjugate reduction may have been considerably greater than indicated by this ratio. [j] A 60:40 mixture of trans–cis stereoisomers, as shown by NMR analysis.

for 43 h (see Table I) indicated that complete reduction of the carbonyl substrate should be feasible since no apparent decomposition of sodium formate had occurred at the high temperature required for this reaction.

Table I contains the results of this reduction for several representative aldehydes and ketones. Since the reaction proceeded more rapidly with aldehydes, we decided to examine the potential use of sodium formate for selective reduction[9] of aldehydes in the presence of ketones. As described in the Experimental Section, treatment of an equimolar mixture of *p*-tolualdehyde and 4-phenyl-2-butanone with sodium formate at 170 °C for 20 h led to 80% reduction of the aldehyde accompanied by >95% recovery of starting ketone.

For polyfunctional substrates that are sensitive to the rather harsh conditions required to effect the selective reduction described above, one of us recently reported[10] a novel reagent ($CH_3CH_2CH(OMgBr)_2$, **1**) that is capable of rapidly reducing aldehydes in the presence of ketones at room temperature. Although the latter reagent (**1**) has limited stability and is less easily manipulated than sodium formate, its low reactivity with a variety of reducible functional groups[11] enhances its value for chemoselective reduction of aldehydes. Both this novel reducing agent (**1**) and sodium formate are unique in that they represent rare examples of reagents possessing a carbon that can function as a hydride donor under *irreversible* conditions.[12]

In view of its low cost and ease of handling, sodium formate offers certain advantages over other reagents[4] used for reduction of carbonyl compounds. Unfortunately, the rather vigorous conditions required for it to function as a hydride donor may restrict its use to reactions involving relatively simple aldehydes and ketones.

Experimental Section

General Procedures. Reactions were carried out under a nitrogen atmosphere. 1-Methyl-2-pyrrolidinone was purchased from Aldrich Chemical Co., Inc., Milwaukee, WI, and used without further purification. Products were recovered from the ether extracts after the organic layer was dried over anhydrous magnesium sulfate and the solvent removed by use of a rotary evaporator under reduced pressure. Evaporative distillation refers to bulb-to-bulb (Kugelrohr) short-path distillation. The NMR spectra were recorded with a Varian EM-360 spectrometer, and infrared spectra were obtained by using a Beckman Acculab 1 spectrophotometer. Vapor-phase chromatography (VPC) was performed on a Hewlett-Packard 5750 chromatograph.

Standard Reduction Procedure. A mixture of 3.0 mmol of aldehyde or ketone, 410 mg (6.0 mmol[13]) of sodium formate, and 500 mg (3.67 mmol) of monobasic potassium phosphate (KH_2PO_4) in 4.0 mL of 1-methyl-2-pyrrolidinone was heated at reflux for the time specified in Table I. The crude product was isolated by dilution of this mixture at room temperature with 50 mL of saturated brine and extraction with ether. The organic layer was washed with 1:1 (v/v) 2 M aqueous hydrochloric acid–saturated brine (2 × 40 mL), 1:1 (v/v) 1 M aqueous sodium hydroxide–saturated brine (1 × 40 mL), and saturated brine (1 × 40 mL) in successive order. The product was isolated from the organic extract in the usual manner and purified by evaporative distillation.

Chemoselective Reduction of *p*-Tolualdehyde in the Presence of 4-Phenyl-2-butanone. A mixture of 360 mg (3.0 mmol) of *p*-tolualdehyde, 455 mg (3.07 mmol) of 4-phenyl-2-butanone, 342 mg (5.03 mmol) of sodium formate, and 494 mg (3.63 mmol) of potassium phosphate monobasic in 4.0 mL of 1-methyl-2-pyrrolidinone was heated at 170 °C (bath temperature) for 20 h. Isolation of the reaction product in the manner described above afforded 736 mg (90%) of material. Subsequent evaporative distillation [bp 40–75 °C (bath temperature, 0.07 mm] gave 608 mg[14] (75%) of a mixture shown by NMR analysis (CHO vs. CH_2OH and $CH_3C{=}O$ vs. CH_3CHOH signals) to contain *p*-tolylcarbinol and unreduced aldehyde in a 4:1 ratio, respectively, and 4-phenyl-2-butanol and the corresponding ketone in a 1:20 ratio, respectively. The fact that 4-phenyl-2-butanone comprised approximately 55% of this product mixture is evidence that aldehydes are somewhat sensitive to destructive side reactions

(9) For previous methods to effect such a transformation, see: Risbood, P. A.; Ruthven, D. M. *J. Org. Chem.* **1979**, *44*, 3969; Andrews, G. C. *Tetrahedron Lett.* **1980**, *21*, 697 and references in footnote 3 in that paper.

(10) Babler, J. H.; Invergo, B. J. *Tetrahedron Lett.* **1981**, *22*, 621.

(11) A full article detailing the sluggish reactivity of this novel reducing agent (**1**) with a variety of functional groups will be submitted for publication in the near future.

(12) The proposed intermediate in a "crossed" Cannizzaro reaction, which bears some resemblance to **1**, is perhaps the best known example of this type of reducing agent. For a review of the Cannizzaro reaction, see: Geissman, T. A. *Org. React.* **1944**, *2*, 94–113.

(13) Since the reduction of ketones occurred quite slowly, 7.5 mmol of sodium formate was used in the reactions involving 4-phenyl-2-butanone and propiophenone.

(14) The rest of the crude product may have been derived from a crossed aldol condensation between the two carbonyl reactants.

under the conditions required for the reduction.

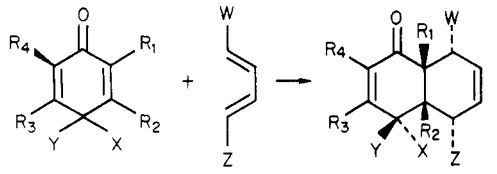
Registry No. *p*-Tolualdehyde, 104-87-0; decyl aldehyde, 112-31-2; cinnamaldehyde, 104-55-2; 4-phenyl-2-butanone, 2550-26-7; propiophenone, 93-55-0; 2-methylcyclohexanone, 583-60-8; 4-methylbenzenemethanol, 589-18-4; decyl alcohol, 112-30-1; cinnamyl alcohol, 104-54-1; 3-phenyl-1-propanol, 122-97-4; 4-phenyl-2-butanol, 2344-70-9; α-ethylbenzenemethanol, 93-54-9; *cis*-2-methylcyclohexanol, 7443-70-1; *trans*-2-methylcyclohexanol, 7443-52-9; sodium formate, 141-53-7; 1-methyl-2-pyrrolidinone, 872-50-4.

Communications

Selective Reactions of Carbanions with *p*-Quinones. The Aggregate Model

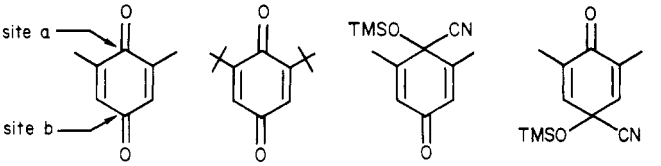
Summary: Additions of carbanions to unsymmetrical *p*-quinones can be achieved at either carbonyl carbon by a judicious choice of reaction conditions.

Sir: Recently, we showed that cross-conjugated cyclohexadienones possessing two different geminal substituents at C4, e.g., **1**, undergo "face-selective" Diels-Alder reactions. Thus, the adducts which result, e.g., **3**, may contain as many as five asymmetric centers but only one relative stereochemistry.[2]



1 **2** **3**

In order to apply this methodology to natural product synthesis, easy access to the various substituted cyclohexadienones, depicted by **1**, is required.[3] Of particular interest here is the availability of quinols (X = OH, Y = alkyl). These compounds are usually prepared by one of three different approaches: (a) exposure of aryl hydroxylamines to strong acid,[4] (b) oxidation of phenols,[5-8] and (c) 1,2-addition of carbanions of *p*-quinones or their synthetic equivalents.[9,10] Methods a and b often produce complex mixtures of products and are therefore of limited applicability. Method c encompasses a broad spectrum of reactions involving quinones and various organometallic reagents. However, most of these processes lack synthetic utility.[9] Recently, Fisher and Henderson[9] reported that reactions of organolithium reagents with *p*-benzoquinones result in the formation of the corresponding quinols in high yield. However, with unsymmetrical quinones these additions exhibit low regioselectivity. In this communication we report that additions of carbanions to unsymmetrical *p*-quinones can be achieved at either carbonyl carbon by a judicious choice of the reaction conditions.



4 **5** **6** **7**

The basic principles that were used to achieve regioselective 1,2-additions of carbanions to *p*-quinones are as follows. If the carbanion in question is made sufficiently bulky by varying its counterion, its degree of aggregation, and/or its degree of solvation, steric factors should dominate the transition state, resulting in regioselective addition to the less hindered carbonyl carbon (site b). By contrast, if the carbanion in question is relatively small and only weakly solvated, electronic factors should dominate the transition state, resulting in regioselective addition to the more electrophilic carbonyl carbon (site a).

Some precedents exist for both the steric and electronic models. For example, Grignard reagents are reported to attack exclusively the less-hindered carbonyl group of extremely hindered quinones, such as **5**, to produce the corresponding quinols in good yield.[11] On the other hand, Evans et al. have previously shown that **4** reacts with trimethylsilyl cyanide to form **6** and **7** in a 94:6 ratio, presumably because the relatively small nucleophile, cyanide ion, preferentially attacks the more electrophilic carbonyl carbon.[12]

In order to test our hypothesis, the following experiments were carried out. Addition of 1 equiv of methylmagnesium bromide to a THF solution of **4** at −78 °C results in the formation of **8** and **9** in 62% and 10% isolated yields, respectively.[13] No trace of **10** is observed. This highly selective, 1,2-addition presumably occurs because methylmagnesium bromide in THF is a relatively large and heavily solvated carbanion, which reacts in accord with the steric model discussed earlier.[14] By contrast,

(1) Fellow of the Alfred P. Sloan Foundation, 1980-1984.
(2) Liotta, D.; Saindane, M.; Barnum, C. *J. Am. Chem. Soc.* **1981**, *103*, 3224.
(3) For an in-depth review of cyclohexadienones, see Waring, A. J. *Adv. Alicyclic Chem.* **1966**, *1*, 129.
(4) Wessely, F.; Holzer, L.; Vilesek, H. *Monatsh. Chem.* **1953**, *84*, 655.
(5) McKillop, A.; Perry, D. H.; Edwards, M.; Taylor, E. C. *J. Org. Chem.* **1976**, *41*, 282.
(6) Ronlan, A.; Parker, V. D. *J. Chem. Soc. C* **1971**, 3214.
(7) Nilsson, A.; Ronlan, A.; Parker, V. D. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2337.
(8) Farrand, J. C.; Johnson, D. C. *J. Org. Chem.* **1971**, *36*, 3606.
(9) Fischer, A.; Henderson, G. N. *Tetrahedron Lett.* **1980**, 701, references cited therein.
(10) (a) Moore, H. W.; Sing, Y. L.; Sidhu, R. S. *J. Org. Chem.* **1980**, *45*, 5057; (b) Moore, H. W.; Sing, Y. L.; Sidhu, R. S. *Ibid.* **1977**, *42*, 3321; (c) Parker, K. A.; Andrade, J. R.; *Ibid.* **1979**, *44*, 3964; (d) Evans, D. A.; Hoffman, J. M. *J. Am. Chem. Soc.* **1976**, *98*, 1983; (e) Evans, D. A.; Wong, R. W. *J. Org. Chem.* **1977**, *42*, 350.
(11) Ershov, V. V.; Bogdanov, G. N.; Voldkin, A. A. *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk* **1963**, 157.
(12) Evans, D. A.; Hoffman, J. M.; Truesdale, L. K. *J. Am. Chem. Soc.* **1973**, *95*, 5822.
(13) The double addition product **9** is presumably produced by an initial Michael addition at C2 (or C6) followed by a subsequent 1,2-addition at C1.
(14) An alternative and complementary argument involves selective activation of the less hindered carbonyl group by complexation with magnesium bromide, which is present as a consequence of the Schlenk equilibrium. Selective Lewis acid complexation with **4** has been previously observed. See: Dickinson, R. A.; Kubela, R.; MacAlpine, G. A.; Stojanc, Z.; Valenta, Z. *Can J. Chem.* **1972**, *50*, 2377.

0022-3263/81/1946-3369$01.25/0