Table I. Reaction of Grignard Reagents with Ethyl Acrylate

$$RX + Mg \rightarrow RMgX$$

$$RMgX + CH_2{=}CHCOOEt \rightarrow RCH_2CH_2COOEt$$

RX	Registry no.	Temp, °C	RCH_2CH_2COOEt[a]	Registry no.	Bp, °C (mm)	Yield, %[b]
Bromobenzene	108-86-1	−20[c]	$PhCH_2CH_2COOEt$	2021-28-5	85 (2)[d]	54
1-Bromopentane	110-53-2	−40	$CH_3(CH_2)_6COOEt$	106-32-1	99 (40)[e]	80
Vinyl bromide	593-60-2	−35 ~ −40[f]	$CH_2{=}CHCH_2CH_2COOEt$	1968-40-7	55 (40)[g]	41
6-Bromo-1-hexene	2695-47-8	−45 ~ −50	$CH_2{=}CH(CH_2)_6COOEt$	35194-39-9	72 (2)[h]	73
Benzyl chloride	100-44-7	−25[c]	$PhCH_2CH_2CH_2COOEt$	10031-93-3	112 (3.5)[i]	69
Cyclohexyl bromide	108-85-0	−45 ~ −50	Ethyl 3-cyclohexylpropanoate	10094-36-7	72 (2)[j]	68

[a] All products gave satisfactory spectroscopic data. [b] Yields given represent distilled product. [c] Cooling below this temperature will cause the Grignard reagent to solidify. [d] Lit.[15] 123 °C (16 mm). [e] Lit.[16] 104 °C (80 mm). [f] −25 °C at onset of the reaction. [g] Lit.[17] 144–146 °C. [h] Lit.[18] 114–116 °C (15 mm). [i] Lit.[19] 130–131 °C (10 mm). [j] Lit.[20] 105–113 °C (17 mm).

is clearly incompatible with the presence of other unsaturation in the molecule. There has been one report of conjugate addition of lithium di-*sec*-butylcuprate to ethyl acrylate giving ethyl 4-methylhexanoate.[2]

In spite of these methods for the extension of a three-carbon chain, the most obvious approach would be the conjugate addition of Grignard reagents with acrylate esters. However, although the 1,4 additions of Grignard reagents to substituted acrylates, such as crotonate, tiglate, and cinnamate, in the presence of copper catalyst under well-defined reaction conditions generally give good to fair yields,[9,10] *sec*-butyl acrylate itself was reported to give only polymerization material.[11]

We reasoned that the key to effecting 1,4 addition to acrylate lay simply in conducting the reaction at low temperature, thus reducing the extent of polymerization. We therefore examined the reactions of ethyl acrylate with Grignard reagents generated from primary, secondary, aryl, benzylic, and vinyl halides and found that it was indeed the case. For example, when ethyl acrylate in ether was added very slowly to a solution of a threefold excess of pentylmagnesium bromide in ether at −40 °C and a catalytic amount of cuprous chloride[12] was added in 13 portions during the course of the reaction, ethyl octanoate could be isolated in 80% yield.[13] Some of our results are given in Table I.

In summary, we feel that the three-carbon homologation is easy to operate and gives good to fair yields with a variety of halides, and we expect that it will find use in synthesis.

Experimental Section

General Reaction Procedure. Ethyl Octanoate. The solution of pentylmagnesium bromide was prepared from 6 g (0.25 g-atom) of magnesium turnings and 37.75 g (0.25 mol) of 1-bromopentane in 400 mL of ether[14] under a nitrogen atmosphere. The solution was cooled to −40 °C and kept at that temperature throughout the reaction. Cuprous chloride[12] (50 mg) was added and then 8.3 g (0.083 mol) of ethyl acrylate in 250 mL of ether was added dropwise over a 3-h period with vigorous stirring. After each 15-min interval during the addition another 50 mg of cuprous chloride was added. After each addition, the system was evacuated and then filled with nitrogen. The last portion was added just after completion of the addition of ethyl acrylate. A total of 650 mg (2.6 mol % with respect to the Grignard reagent) of cuprous chloride was used. The cooling bath was then removed and the reaction mixture was stirred at ambient temperature for 30 min and at room temperature for 20 min. The dark solution was poured rapidly into a mixture of crushed ice and concentrated hydrochloric acid with vigorous stirring. The aqueous solution was separated and extracted with ether. The combined ether extracts were washed with saturated sodium bicarbonate, water, and with saturated brine, then dried ($MgSO_4$), filtered, and concentrated. The residue was distilled to yield 11.4 g (80%) of pure ethyl octanoate, bp 99 °C (40 mm) [lit.[16] 104 °C (80 mm)]. The product was identified by comparison of its infrared and NMR spectra and its VPC behavior with those of an authentic sample.

Acknowledgment is made to the Stanford Research Institute for financial support of this work.

Registry No.—$CH_2{=}CHCOOEt$, 140-88-5.

References and Notes

(1) (a) E. J. Corey and K. Achiwa, *Tetrahedron Lett.*, 1837 (1969); (b) E. J. Corey, K. Achiwa, and J. A. Katzenellenbogen, *J. Am. Chem. Soc.*, **91**, 4318 (1969).
(2) C. P. Casey, C. R. Cyr, and J. A. Grant, *Inorg. Chem.*, **13**, 910 (1974).
(3) R. E. Atkinson, R. F. Curtis, D. M. Jones, and J. A. Taylor, *J. Chem. Soc. C*, 2173 (1969).
(4) R. F. Heck and J. P. Nolley, *J. Org. Chem.*, **37**, 2320 (1972).
(5) P. D. Bartlett, S. J. Tauber, and W. P. Weber, *J. Am. Chem. Soc.*, **91**, 6362 (1969).
(6) E. J. Corey and D. E. Cane, *J. Org. Chem.*, **35**, 3405 (1970).
(7) E. J. Corey, C. U. Kim, R. H. K. Chen, and M. Takeda, *J. Am. Chem. Soc.*, **94**, 4395 (1972).
(8) E. J. Corey and D. J. Beames, *J. Am. Chem. Soc.*, **94**, 7210 (1972).
(9) J. Munch-Petersen, *Bull. Soc. Chim. Fr.*, 471 (1966), and references cited therein.
(10) G. H. Posner, *Org. React.*, **19**, 1 (1972).
(11) J. Munch-Petersen, *Acta Chem. Scand.*, **12**, 967 (1958).
(12) Commercial cuprous chloride was used.
(13) The conjugate addition conducted at −40 °C in the absence of copper catalyst was not successful.
(14) Vinylmagnesium bromide was prepared in tetrahydrofuran.
(15) R. C. Weast, "The Handbook of Chemistry and Physics", 57th ed, Chemical Rubber Publishing Co., Cleveland, Ohio, 1976–1977, p C-459.
(16) Reference 15, p C-406.
(17) "Dictionary of Organic Compounds", 4th ed, Oxford University Press, New York, N.Y., 1965, p 2635.
(18) Reference 17, p 2527.
(19) Reference 17, p 2678.
(20) P. L. de Benneville and R. Connor, *J. Am. Chem. Soc.*, **62**, 283 (1940).

Chromium(VI) Oxidations of Secondary Alcohols in the Presence of Amino Groups, or How to Solubilize Chromium(III) in Base

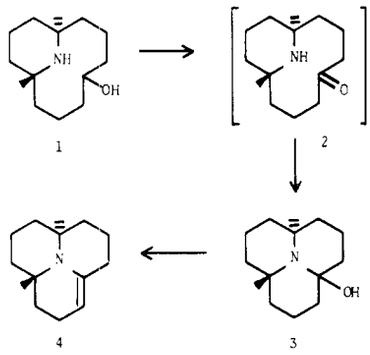
Richard H. Mueller* and Robert M. DiPardo

Department of Chemistry, Yale University, New Haven, Connecticut 06520

Received April 6, 1977

We wish to report a method for the facile solubilization of Cr(III) in basic water; this method conveniently overcomes serious product isolation difficulties in the oxidation of alcohols containing amino groups.

In connection with another problem, we recently desired to effect transformation of the amino alcohol **1** to the amino ketone **2** (actually expected to exist as the carbinolamine **3** or the enamine **4**).[1] We wished to perform this oxidation under acidic conditions for several reasons: to protect the amino



group from oxidation and to prevent conversion of the product to the enamine 4 (expected to be very sensitive to oxidation) in the presence of the oxidizing agent. Only after oxidation of the alcohol was complete and after excess oxidant was destroyed would the amino ketone 2 be liberated by base and allowed to condense to 4. Our first choice method for this conversion was oxidation with the Jones reagent;[2] Cr(VI) oxidations generally give high yields, are usually fast and complete, and are experimentally simple and inexpensive.[3] In practice, oxidation of 1 by Jones reagent in acidic aqueous acetone appeared to work well, but the isolation of the product was exceptionally tedious. Addition of base to the reaction mixture after destruction of excess oxidant resulted in formation of Cr(III) hydroxide, a thick, gelatinous precipitate, difficult if not impossible to filter; attempted extraction of this suspension with ether resulted in a stable emulsion. Also, some of the product was undoubtedly adsorbed and/or entrapped by the precipitate. All in all, a single experience with this almost intractable workup method was sufficient to prompt a search for an alternative workup procedure.

We reasoned that if the Cr(III) could be complexed by an appropriate ligand (e.g., trisodium citrate), the Cr(III) would be solubilized in the basic medium and thus not interfere with the isolation of the product. However, addition of trisodium citrate to the reaction mixture followed by addition of NaOH after 1 h resulted in the same thick precipitate of Cr(III) hydroxide. The lack of complexation is due to the well-known (at least among inorganic chemists) reluctance of Cr(III) to exchange ligands at a reasonable rate.[4] On the other hand, Cr(II) exchanges ligands quickly[4] and, in fact, can catalyze the exchange of ligands by Cr(III).[5] Thus, trisodium citrate *and* a small piece of amalgamated mossy Zn were added to the reaction mixture after oxidation was complete and excess oxidant was consumed; after 10 min at 25 °C under N_2, addition of excess NaOH resulted in a clear, dark solution from which the product was extracted without difficulty. With this workup procedure, the enamine 4 can be obtained in 80% isolated yield by oxidation of the amino alcohol 1.

The presumed mechanism for the Cr(II)-catalyzed Cr(III) ligand exchange process is shown below.

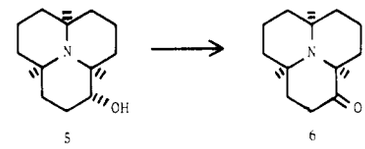
$$Zn(Hg) + 2Cr(III) \rightarrow Zn(II) + 2Cr(II) \quad (1)$$

$$Cr(II) + nL \rightarrow Cr(II)L_n \quad (2)$$

$$Cr(II)L_n + Cr(III) \rightarrow Cr(III)L_n + Cr(II) \quad (3)$$

The amalgamated zinc serves to generate a small amount of Cr(II) (step 1), which then exchanges ligands quickly (step 2). Electron transfer then occurs rapidly (step 3) to generate a complexed Cr(III) and a fresh Cr(II), ready to reenter the cycle at step 2. Eventually all the Cr(III) is complexed in a base-soluble form under mild conditions. An important feature is that only a catalytic amount of Cr(II) suffices to complete the exchange within a short time.

We have also oxidized amino alcohol 5 to the amino ketone 6. Oxidation of 5 under conditions described for 1 was slow and



incomplete. A procedure using Jones reagent in glacial acetic acid resulted in faster reaction.

Na_2EDTA may be used in place of the trisodium citrate with equal efficacy; we prefer the citrate as it is less expensive and more easily handled.

This workup procedure should also be applicable to other reactions in which Cr(III) is generated and a basic workup is desired.

Experimental Section

Infrared spectra were obtained of liquid films between KCl plates with a Perkin-Elmer 727 spectrophotometer. ^1H NMR spectra were obtained of $CDCl_3$ solutions with a Perkin-Elmer R32 spectrometer; chemical shifts are reported in parts per million downfield from internal tetramethylsilane. The sweep width was calibrated with internal $CHCl_3$ taken as δ 7.24. Combustion analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich. Vapor-phase chromatography was performed with a Perkin-Elmer 880 flame ionization or a Varian 1400 thermal conductivity instrument. Columns used were 5% OV-1 and 1.5% OV-101 on Chromosorb G and 3% OV-225 on Gas-Chrom Q.

Oxidation of 13-Azabicyclo[7.3.1]tridecan-5-ol (1) to *trans*-1,2,3,3a,4,5,6,6a,7,8-decahydropyrido[2.1.6-*de*]quinolizine (4). 1[1] (2.65 g, 13.5 mmol) was dissolved in 15 mL of acetone in a 250-mL round-bottom flask. The flask was placed in an ice/water bath and 6 mL (18 mmol) of 3 M H_2SO_4 was added over 3 min with magnetic stirring. Then 4 mL of Jones reagent [10.7 mmol Cr(VI), 20% excess] was added over 3 min. After 15 min, the initial red-orange solution had become a yellow-green suspension; the ice/water bath was removed and the mixture was stirred another 15 min. Excess oxidant was destroyed by addition of 2 mL of *i*-PrOH to give a blue-green suspension within 5 min. Water (50 mL) was added along with 15 g (51 mmol) of trisodium citrate. The flask was flushed with Ar and a small piece of amalgamated mossy Zn (140 mg) was added. After 10 min, 50 mL of Et_2O was added and the reaction mixture was made strongly basic with 20% aqueous NaOH solution (about 15 mL). The very dark but clear water layer was separated and extracted with three 50-mL portions of Et_2O. The combined organic layer was washed with 5 mL of saturated aqueous Na_2SO_4 solution and dried over solid Na_2SO_4. The solvent was removed in vacuo to afford a light yellow solid, presumably the carbinolamine 3. Dehydration was effected by refluxing 15 min in hexane under a Dean–Stark trap. The hexane was removed in vacuo and the resulting yellow oil was bulb-to-bulb distilled [80 °C (0.2 mm)] to afford 1.91 g (80% yield) of the enamine 4 as a clear, colorless liquid, identical with material prepared by another route.[6] TLC (silica gel, 10 mL of THF + 2 drops of concentrated NH_4OH) showed the absence of starting alcohol; TLC and VPC (OV-1, -101, -225) indicated a purity of 99%. The enamine discolors in air; it is best stored sealed in glass or as a salt: IR (film) 3050, 2935, 2865, 2800, 1655 cm^{-1}; NMR δ 4.70 (1 H, br s), 3.05 (1 H, dd, J = 6, 12 Hz), 2.40 (1 H, mult). Anal. Calcd for $C_{12}H_{19}N$: C, 81.30; H, 10.80; N, 7.90. Found: C, 81.24; H, 10.80; N, 7.88.

Oxidation of (1β,3aα,6aα,9aα)-Dodecahydropyrido[2.1.6-*de*]quinolizin-1-ol (5) to (3aα,6aα,9aα)-Decahydropyrido-[2.1.6-*de*]quinolizin-1(2*H*)-one (6). Amino alcohol 5[7] (565 mg, 2.9 mmol) was dissolved in 5.8 mL of HOAc in a 100-mL round-bottom flask equipped with a magnetic stirring bar. Concentrated H_2SO_4 (0.16 mL, 2.9 mmol) was added all at once followed by 1.1 mL of Jones reagent [2.9 mmol Cr(VI), 50% excess] over 5 min. After 30 min, 1 mL of *i*-PrOH was added to consume the excess oxidant. After dilution of the mixture with 17 mL of water, 2.52 g (8.6 mmol) of trisodium citrate was added along with a small piece of amalgamated mossy Zn. The flask was flushed with N_2. After 10 min, the mixture was made strongly basic with aqueous NaOH and then extracted with five 20-mL portions of Et_2O. The combined extract was diluted with hexane, washed with saturated aqueous NaCl solution, and dried over Na_2SO_4. After removal of the solvent in vacuo, the pale yellow oil obtained was bulb-to-bulb distilled [ca. 85 °C (0.2 mm)] to give 495 mg (85% yield) of the amino ketone 6 as a clear oil. VPC (OV-101) and TLC (silica gel, 4:1 cyclohexane/EtOAc and 99:1 Et_2O/NH_4OH) indicated a trace (~1%) of remaining alcohol with no other detectable impurities: IR 2959, 2865, 2790, 2730, 1725 cm^{-1}; NMR, no peaks

below δ 2.65 ppm. The analytical sample was obtained by silica gel chromatography (cyclohexane/EtOAc) followed by bulb-to-bulb distillation. Anal. Calcd for $C_{12}H_{19}NO$: C, 74.57; H, 9.91; H, 7.25. Found: C, 74.53; H, 9.92; N, 7.22.

Acknowledgments. We thank Professor J. W. Faller of this Department for helpful discussions, E. I. DuPont de Nemours Co. for a Young Faculty Grant, and the National Science Foundation and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for financial support.

Registry No.—**1**, 61714-12-3; **3**, 62930-44-3; **4**, 57147-61-2; **5**, 62930-45-4; **6**, 62930-46-5; Cr, 7440-47-3.

References and Notes

(1) R. H. Mueller, *Tetrahedron Lett.*, 2925 (1976).
(2) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).
(3) Review: K. B. Wiberg in "Oxidation in Organic Chemistry", Vol. A, K. B. Wiberg, Ed., Academic Press, New York, N.Y., 1965, Chapter 2.
(4) F. A. Cotton and G. Wilkinson, "Advanced Inorganic Chemistry", 3rd ed, Interscience, New York, N.Y., 1972, pp 834–838.
(5) Reference 4, p 679; H. Taube and E. S. Gould, *Acc. Chem. Res.*, **2**, 321 (1969); C. L. Robinson in "Comprehensive Inorganic Chemistry", Vol. 3, Pergamon Press, Oxford, 1973, pp 660–664 and 675–676.
(6) R. H. Mueller and R. M. DiPardo, *J. Chem. Soc., Chem. Commun.*, 565 (1975).
(7) Amino alcohol **6** was prepared by hydroboration–oxidation of the enamine[8] *cis*-1,2,3,3a,4,5,6,6a,7,8-decahydropyrido[2.1.6-*de*]quinolizine.[6]
(8) I. J. Borowitz and G. J. Williams, *J. Org. Chem.*, **32**, 4157 (1967).

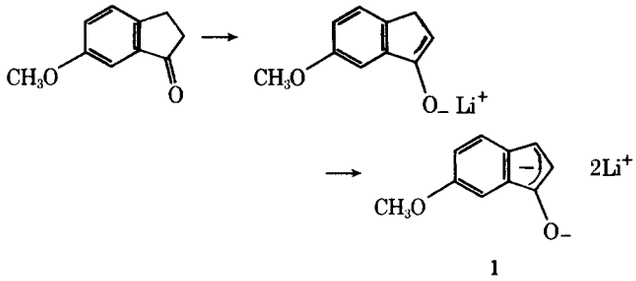
Generation and Alkylation of the Dianion (Homoenolate) of a 1-Indanone

Barry M. Trost* and Lee H. Latimer

Department of Chemistry, University of Wisconsin, Madison, Wisconsin 53706

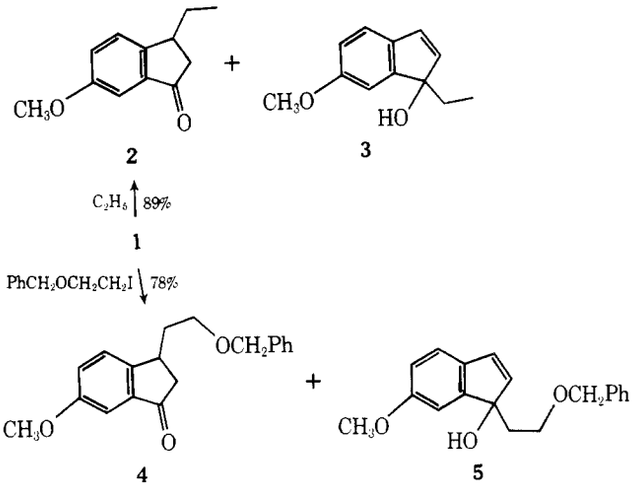
Received March 21, 1977

The generation of dianions from monofunctional compounds has been seldom observed and utilized.[1] In conjunction with the chemistry of gibberillins, we required a facile route to 3-substituted 1-indanones. Metalation of the enamines of 1-indanones followed by alkylation does provide access to such compounds.[2] However, a more direct method was envisioned based upon the fact that the enolate of indanone is an oxyindene which should still be reasonably acidic as a result of the generation of the aromatic indenyl anion. We wish to report the facile direct generation of the homoenolate of 1-indanone and its utility in forming both 3-monosubstituted and 2,3-disubstituted 1-indanones.

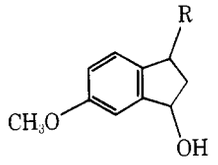


1

Treatment of 6-methoxy-1-indanone[3] with 2 equiv of lithium diisopropylamide at −78 °C in THF produced a white suspension in a yellow solution, which turned deep red upon warming to 0 °C for 4 h. Addition of 1 equiv of ethyl iodide followed by aqueous workup gave a 89% yield of 3-ethyl-1-indanone (**2**) and <3% of 3-ethyl-3-hydroxy-1-indene (**3**).



Similar results were obtained upon alkylation with 2-benzyloxyethyl iodide. The assignment of the 3-substitution for **2** and **4** follows from NMR spectra of the compounds and that of their corresponding alcohols **6** and **7**, respectively.



6, R = C_2H_5
7, R = $PhCH_2OCH_2CH_2$

In the starting indanone, the protons at C(2) and C(3) appear at δ 2.66 and 3.05, respectively. In **2** and **4** the absorptions for the benzylic protons appear as a multiplet at δ 3.20 and 3.44, respectively, for one proton each and the methylene groups α to the carbonyl groups appear as a clean doublet of doublets [**2**, δ 2.23 (J = 19, 4 Hz) and 2.74 (J = 19, 7 Hz); **4**, δ 2.32 (J = 19, 3 Hz) and 2.76 (J = 19, 7 Hz)]. In **7** the proton α to the hydroxyl group appears as a doublet of doublets (J = 8, 5 Hz) at δ 5.1 in the presence of D_2O which demands a methylene group at C(2). Further transformations of these compounds reaffirm these conclusions.[4]

While full characterization of the trace by-products was not obtained, spectral data clearly suggest the assigned structures, **3** and **5**. The infrared spectra show the presence of an alcohol group, but the absence of any carbonyl group. The NMR spectra are essentially first order. For example, **5** shows a clean AB pattern for the vinyl protons (δ 6.44 and 6.19, J = 6 Hz) and a single high-field methylene group comprised of diastereotopic protons coupled only to an adjacent methylene group—each proton is a doublet (J = 15 Hz) of triplets (J = 7 Hz) at δ 2.20 and 1.89. Reaction at C(1) of **1** points out the analogy to **8**[5] and **9**,[1h,i] in which the problem of α vs. γ attack

8 9

is well recognized. In contrast to **8**, X = alkyl or silyl, **1** should and does show almost exclusive γ attack due to the electronic repulsion of the charged oxygen, which will be reinforced by the preference to maintain maximum charge stabilization by delocalization in the initial product.

Since the initial product is an enolate, further substitution is quite feasible. Indeed, after alkylation of **1** with benzyloxyethyl iodide, addition of diphenyl disulfide[6] led to the 2,3-disubstituted product **10**. Based upon the fact that the base is the limiting reagent under these conditions, **10** was obtained in 84% yield. The substitution of the phenylthio group at C(2)