Tetrahedron Vol 37, pp. 2091 to 2096, 1981
Printed in Great Britain.

0040-4020/81/112091-06$02.00/0

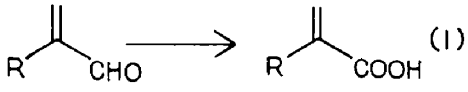
OXIDATION OF α,β-UNSATURATED ALDEHYDES

BALKRISHNA S. BAL, WAYNE E. CHILDERS, JR. and HAROLD W. PINNICK*
Department of Chemistry, University of Georgia, Athens, Georgia 30602

(Received in USA 23 February 1981)

Abstract - A variety of methods for the conversion of α,β-unsaturated aldehydes to the corresponding acids have been explored. The best approach uses sodium chlorite and gives the desired transformation even in systems where steric hindrance and/or sensitive functionality are present.

In a recent investigation,[1] the oxidation of α-methylene aldehydes to the corresponding acids was required (eq 1). Because of the

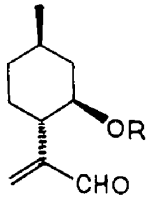


(1)

sensitivity of the molecules of interest, strong oxidizing agents like Jones reagent[2] and potassium permanganate[3] were not appropriate. In addition, the use of silver oxide[4,5] was to be avoided because of the high initial investment and the bothersome recycling of silver which is necessary for economic reasons.

Several methods have been developed for the oxidation of α,β-unsaturated aldehydes to the corresponding acids or esters.[5,6] The procedure employing Caro's acid[6a] has been applied to acrolein, methacrolein and crotonaldehyde only. In addition, the necessary reagent is prepared with concentrated sulfuric acid and this may cause problems with sensitive molecules. A second very clever method was developed by Corey[5a] based on the in situ formation of a cyanohydrin which undergoes oxidation by manganese dioxide to give an acyl cyanide. In the presence of an alcohol, the ester is isolated. Alternatively, silver (II) oxide converts the cyanohydrin into the unsaturated acid. A recent modification treats the trimethylsilyl protected cyanohydrins of α,β-unsaturated aldehydes with pyridinium dichromate.[6b] Allylic oxidation also occurs so that Δ^2-butenolides are isolated. No α-methylene aldehydes were oxidized by either of these methods using cyanohydrins. Another approach uses selenium dioxide[6c] but requires 90% hydrogen peroxide and thus presents some danger particularly with large scale reactions. Finally, cinnamaldehyde has been oxidized via the corresponding dithiane anion[6d] and oxime.[6e] We now wish to report the results of a detailed study of the reaction of equation 1.

The first method which was examined was that developed by Corey.[5a] Consequently, citral was converted into the corresponding methyl ester without difficulty; however, when the α-methylene aldehyde 1 (R=$C_6H_5CH_2$) was allowed to react according to the prescribed directions, a variety of products resulted. These included compounds derived from conjugate addition of cyanide ion.

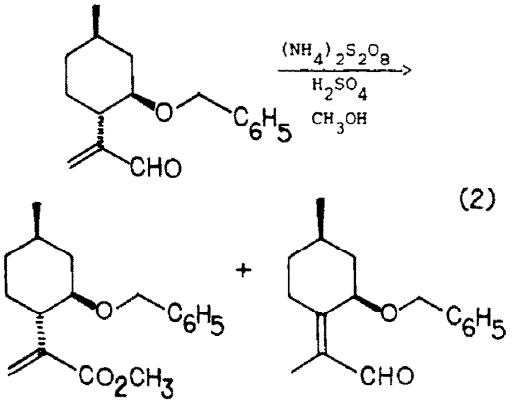


1

In view of the unusual regioselectivity for 1,2-addition in the reaction of trimethylsilyl cyanide (TMSCN) with enones,[7] it was felt that a modification of Corey's procedure may improve its general synthetic utility by increasing the scope of the reaction.[8] Indeed, TMSCN reacts with a variety of aldehydes to give good yields of the trimethylsilyl-protected cyanohydrins which react with manganese dioxide[9] in methanol containing acetic acid to yield the corresponding methyl esters (see Table I). In many cases, a cleaner product can be obtained if the oxidation is run in benzene as a solvent. In addition, the cyanohydrin can be liberated by deprotection of the TMSCN product and then allowed to react with manganese dioxide. These changes reduce the amount of unreacted aldehyde which sometimes is obtained. Nevertheless, all attempts to oxidize aldehyde 1 (R=$C_6H_5CH_2$)[10]

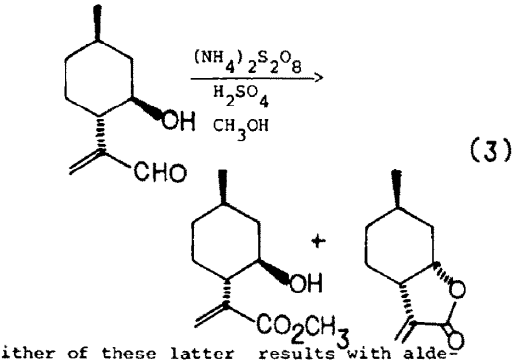
via the cyanohydrin gave significant amounts (typically 50%) of recovered starting material in addition to the desired methyl ester.

The ammonium persulfate procedure[6a] was studied next.[11] Despite the use of concentrated sulfuric acid to prepare the reagent, a 90% yield of methyl cinnamate is obtained from cinnamaldehyde. Oxidation of aldehyde 1 ($R=C_6H_5CH_2$) gives an 83% yield of a 1:1 mixture of the desired ester and isomerized starting material (eq 2).[12] The free alcohol 1 (R=H) gives an 87% yield of the



(2)

corresponding ester contaminated with the α-methylene lactone (eq 3).[13]



(3)

Neither of these latter results with aldehyde 1 are acceptable for the intended goals.

Another method for the oxidation of aldehydes employs sodium chlorite in the presence of various chlorine scavengers[14] but this has never been applied to α-methylene aldehydes. With 2-methyl-2-butene as the chlorine trap,[14b] a 95% yield of cinnamic acid is isolated. Even more significant is the result from aldehyde 1 ($R=C_6H_5CH_2$) where a 90% yield of pure acid is obtained.

In addition, oxidation of citral (65/35 mixture of E and Z isomers) gives the corresponding acid as a 71/29 mixture of E/Z isomers.[15] Consequently, the oxidation reaction is stereospecific. The results using sodium chlorite are summarized in Table II.

In summary, numerous methods for the oxidation of α,β-unsaturated aldehydes have been explored. Only sodium chlorite works well with sensitive substrates containing the α-methylene aldehyde unit. This reagent effects clean oxidations quickly and in a stereospecific manner. In addition, it is very inexpensive. This method has considerable synthetic potential.

EXPERIMENTAL SECTION

All reactions involving air-sensitive reagents were run under nitrogen in flamed-out apparatus. Proton NMR spectra were run on Varian T-60 or EM-390 spectrometers. Infrared spectra were recorded on Perkin-Elmer model 297 or 599B spectrophotometers. Mass spectra were obtained with a Finnigan 4023 GC/MS.

Typical procedures for oxidations are provided.

Oxidation of E- 2,4-dimethyl-2-hexenal via the cyanohydrin

The aldehyde (1.26 g, 10.0 mmol) was refluxed with 1.4 g (14 mmol) of freshly distilled TMSCN and 1 mg of anhydrous zinc iodide overnight. Distillation of the product gave 2.15 (95%) of the siloxynitrile: BP 52-57°C (0.2 mm); NMR (CCl_4) δ 0.1 (s, 9H), 0.8-1.4 (m, 8H), 1.6-1.8 (m, 4H), 4.6 (s, 1H), 5.2 (m, 1H); IR (NaCl) 2950, 2220, 1460, 1250, 1070, 860, 840 cm^{-1}.

The siloxynitrile (2.15 g, 9.50 mmol) was stirred at room temperature overnight with 10 ml of 10% HCl and 50 ml of THF. The reaction mixture was poured into water and extracted with three 20 ml portions of ether which gave 1.5 g (98%) of the cyanohydrin after drying and concentration: NMR (CCl_4) δ 0.8-1.5 (m, 8H), 1.6-2.0 (m, 4H), 4.3 (br s, 1H), 4.7 (s, 1H), 5.5 (d, J = 8 Hz, 1H); IR (NaCl) 3420, 2960, 2240, 1460, 1040, 1020 cm^{-1}.

The cyanohydrin (1.5 g, 9.5 mmol) was dissolved in 70 ml of dry benzene and 3 ml of methanol containing 5 drops of glacial acetic acid. Manganese dioxide (6.0 g, 69 mmol) was added and the reaction mixture was

allowed to stir overnight at room temperature. The reaction mixture was filtered through celite, diluted with water and extracted with three 30 ml portions of ether. The combined ether layers were dried and concentrated to give, after distillation, 1.4 g (90%) of methyl E-2,4-dimethyl-2-hexenoate: BP 100-110° (40 mm); NMR (CCl_4) δ 0.8-1.5 (m, 8H), 1.6-2.0 (m, 4H), 3.6 (s, 3H), 6.4 (d, J = 10 Hz, 1H); IR (NaCl) 2960, 1715, 1650, 1430, 1270, 1240, 1150, 1090, 740.

Oxidation of Aldehyde 1 (R=H) with Caro's Acid

Caro's acid was prepared by adding 3.0 g (13 mmol) of ammonium persulfate in portions to 3.5 g of concentrated sulfuric acid such that the temperature was maintained below 15°C. This solution was added dropwise to a solution of aldehyde 1 (0.83 g, 5.0 mmol) dissolved in 15 ml of methanol at 0°C. The reaction mixture was stirred for 6 hours at 0°C, diluted with 50 ml of water and extracted with three 30 ml portions of ether. The combined ether layers were dried and concentrated to give, after bulb to bulb distillation, 0.71 g of a mixture of the corresponding ester and the cis-α-methylene lactone: BP 170-173°C (3.1 mm); NMR (CCl_4) δ 3.7 (s, 3H, CO_2CH_3), 5.5 (s, 1H, $CH=CCO_2CH_3$), 6.1 (s, 1H, $CH=CCO_2CH_3$), 5.3 (s, 1H, $CH=C-CO_2$), 5.9 (s, 1H, $CH=CCO_2$); IR (NaCl) 3450, 2930, 2850, 1773, 1720, 1628, 1435 cm^{-1}; GC/MS m/e (ester) 198, 181, 166, 149, 138, 120, 110, 94, 81, 67, 53, 41 (lactone) 166, 138, 94, 67, 53, 41, 39. The ratio of ester to lactone was approximately 80:20 by GC and NMR.

Oxidation of Aldehyde 1 ($R=C_6H_5CH_2$) with Sodium Chlorite

The aldehyde (0.30 g, 1.2 mmol) was dissolved in 25 ml of tert-butyl alcohol and 6 ml of 2-methyl-2-butene.[16] A solution of sodium chlorite (1.0 g, 11 mmol) and sodium dihydrogenphosphate (1.0 g, 8.3 mmol) in 10 ml of water was added dropwise over a 10 minute period. The pale yellow reaction mixture was stirred at room temperature overnight. Volatile components were then removed under vacuum, the residue was dissolved in 30 ml of water and this was extracted with two 15 ml portions of hexane. The aqueous layer was acidified to pH 3 with HCl and extracted with three 20 ml portions of ether. The combined ether layers were washed with 50 ml of cold water, dried and concentrated to give 0.20 g (90%) of a pale yellow oil which was identified as the desired acid: NMR (CCl_4) δ 0.8-2.8 (m, 11H), 3.2-3.8 (m, 1H), 4.3 (AB q, J_a = 5 Hz, J_b = 28 Hz, 2H), 5.4 (s, 1H), 6.2 (s, 1H), 7.1 (s, 5H), 9.4 (br s, 1H); IR (NaCl) 3600-2400, 1690, 1620, 1450, 1280, 1100, 1060, 690 cm^{-1}.

ACKNOWLEDGMENT We thank Professor R. K. Hill for providing a generous sample of E-2,4-dimethyl-2-hexenal as well as spectral data on the corresponding oxidation product.

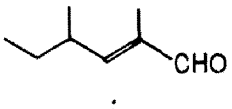
REFERENCES AND NOTES

1. B. S. Bal and H. W. Pinnick, submitted to J. Org. Chem.
2. K. Bowden, I. M. Heilbron, E.R.H. Jones and B.C.L. Weedon, J. Chem. Soc., 39 (1946). α,β-Unsaturated aldehydes are fairly resistant to Jones oxidation[1] (K. E. Harding and R. C. Ligon, Syn. Comm., 4, 297 (1974)). In fact, primary allylic alcohols and benzylic alcohols give aldehydes when reacted with Jones reagent: K. E. Harding, L. M. May and K. F. Dick, J. Org. Chem., 40, 1664 (1975).
3. Potassium permanganate oxidizes both aliphatic and aromatic aldehydes to acids but also will attack the double bond of α,β-unsaturated acids: D. G. Lee and J. R. Brownridge, J.Am.Chem.Soc., 95, 3033 (1973); K. B. Wiberg, C. J. Deutsch and J. Rocek, J.Am.Chem.Soc., 95, 3034 (1973).
4. J. A. Marshall and N. Cohen, J. Org. Chem., 30, 3475 (1965). Note that the preparation of silver oxide where the product is washed free of base (as in K.G.A. Busch, J.W.Clark, L.B. Genung, E.F. Schroeder and W.L.Evans, J.Org.Chem., 1, 1 (1936)) is not of any value here. The mixture of silver oxide and base as in Marshall's paper and in E.Campaigne and B.F.Tullar, Org.Syn., Coll.Vol.IV, 921 (1963) is necessary.
5. (a) E. J. Corey, N. W. Tilman and B. E. Ganem, J.Am.Chem.Soc., 90, 5616 (1968). (b) Cinnamaldehyde is oxidized to cinnamic acid by reaction with silver (II) oxide and sodium cyanide.

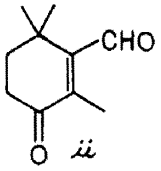
6. (a) A Nishihara and I. Kubota, J. Org. Chem., 33, 2525 (1968). (b) E. J. Corey and G. Schmidt, Tetrahedron Lett., 731 (1980). (c) C. W. Smith and R. T. Holm, J. Org. Chem., 22, 746 (1957); R. Kazlauskas, J. T. Pinhey, J. J. H. Simes and T. G. Watson, J. Chem. Soc., Chem. Comm., 945 (1969). (d) R. A. Ellison, W. D. Woessner and C. C. Williams, J. Org. Chem., 37, 2757 (1972). (e) H. Rapoport and W. Nilsson, J. Org. Chem., 27, 629 (1962).

7. D. A. Evans, G. L. Carroll and L. K. Truesdale, J. Org. Chem., 39, 914 (1974).

8. (a) The aldehyde i fails to oxidize when the Corey procedure[5a] is used: G. H. Morton, Ph.D. dissertation, University of Georgia, 1980, p. 7. (b) Another hindered aldehyde (ii) can be oxidized to the corresponding methyl ester in 80% crude yield. This is the only example known to the authors of successful oxidation of a hindered aldehyde by this method. We thank Dr. Armand B. Pepperman for details of this conversion.



i



ii

9. Prepared by the method of Attenburrow: J. Attenburrow, A.F.B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A.B.A. Jansen and T. Walker, J.Chem.Soc., 1094 (1952).

10. The free alcohol 1 (R=H) forms an unidentified compound when allowed to react with TMSCN.

11. We thank Professor Wolfgang Kreiser for pointing out this method.

12. The structural assignments are based on ^{1}H NMR, IR and GC/MS data.

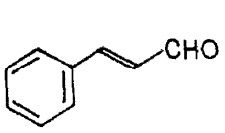
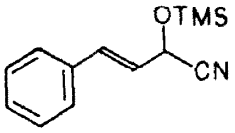
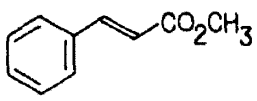
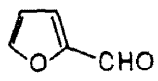
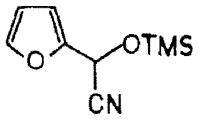
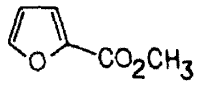
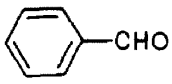
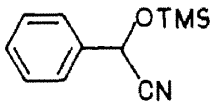
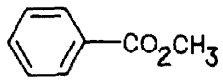
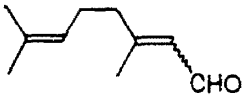
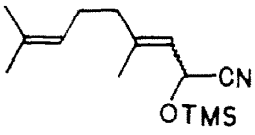
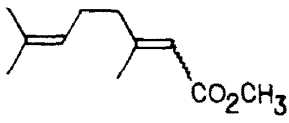
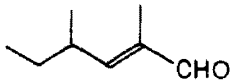
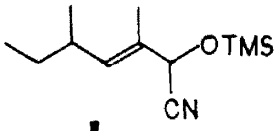
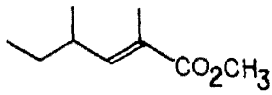
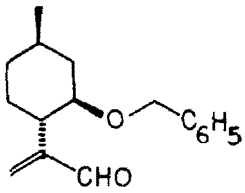
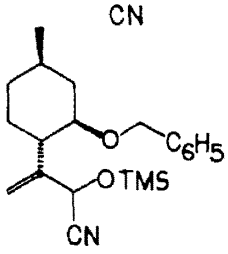
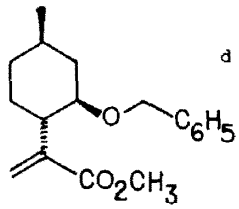
13. These assignments are based on comparison of the ^{1}H NMR spectrum of the mixture with spectra of authentic compounds.[1]

14. (a) B. O. Lindgren and T. Nilsson, Acta Chem. Scand., 27, 888 (1973). (b) Kraus has recently reported the use of 2-methyl-2-butene to take up the chlorine: G.A. Kraus and M.J.Taschner, J.Org.Chem., 45, 1175 (1980); G. A. Kraus and B. Roth, J. Org. Chem., 45, 4825 (1980).

15. The amounts of E and Z isomers were determined by GC analysis on a QF-1/carbowax column. The acids were analyzed as the methyl esters. We thank Dr. Richard R. Hautala for determining these ratios.

16. We thank the Shell Chemical Company for a generous sample of "t-amylene".

TABLE I. OXIDATION OF ALDEHYDES VIA CYANOHYDRINS[a]

ALDEHYDE	SILOXYNITRILE (% YIELD)[b]		ESTER (% YIELD)	
		(97)		(90)
		(98)		(92)
		(98)		(87)
		(90)		(83)
		(95)		(88)[c]
		(87)		[d]

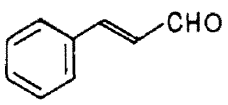
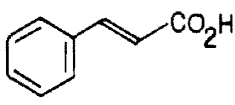
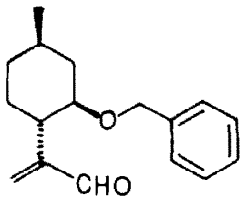
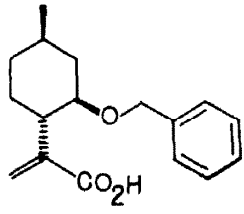
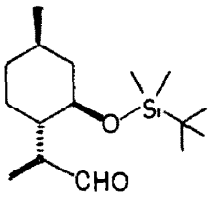
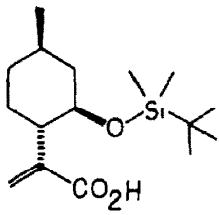
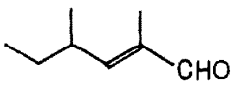
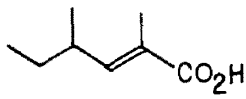
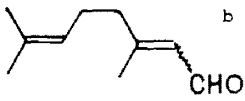
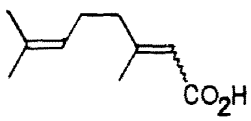
[a] All yields refer to products purified by distillation.

[b] Prepared from the aldehydes with TMSCN under ZnI_2 catalysis.

[c] The cyanohydrin was prepared by deprotection with dilute HCl (98%) and oxidation with MnO_2 in benzene containing methanol gave the ester (90%).

[d] This ester was contaminated with at least 50% of the starting aldehyde.

TABLE II. OXIDATION OF ALDEHYDES WITH SODIUM CHLORITE[a]

ALDEHYDE	ACID (% YIELD)	
		(95)
		(90)
		(87)
		(90)
 [b]		(92)[c]

[a] All products are distilled or recrystallized.

[b] E/Z = 65/35

[c] E/Z = 71/29 (determined on methyl esters)