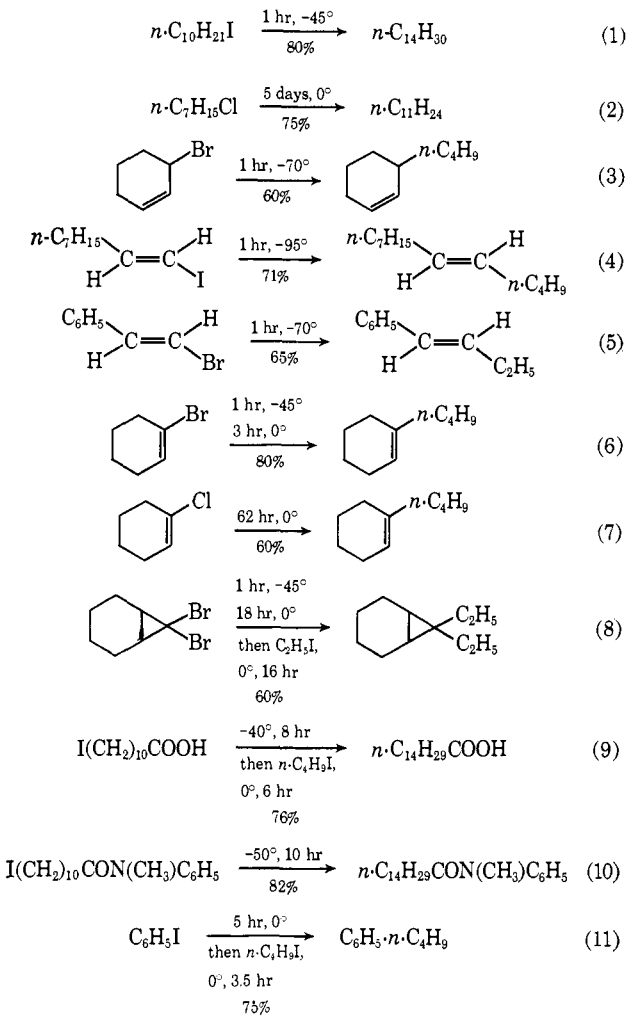

yields of the products shown in (8) and (11) were *ca.* 10 and 30%, respectively. The following by-products were observed in the above reactions: cyclohexene (10%) in reaction 3, 1-nonene (15%) and 8,10-octadecadiene (5%) in reaction 4, styrene (15%) and *trans,trans*-1,4-diphenylbutadiene (10%) in reaction 5, 7-ethylnorcarane (20%) in reaction 8, and benzene (20%) in reaction 11. Clearly, the principal side reaction in these cases is due to replacement of halogen by metal followed by protonation during the usual aqueous work-up. This side reaction may become dominant as, for example, with α-bromo ketones. Elimination may also be a major reaction pathway as with cyclohexyl iodide, which affords only cyclohexene. In general, the selection of experimental conditions is more critical with *n*-alkylcopper reagents than with lithium dimethylcopper as a result of these complications.[9]

There also appears to be a marked effect of temperature on the reactions of lithium dialkylcopper reagents, and in many cases an optimum point can be located, above and below which yields of cross-coupling product diminish. In our experience the optimum temperature tends to increase (within the over-all range −95 to 0°) with decreasing reactivity of the halide, approximately in the order >C=CH(I,Br), RCH_2CH_2I, >C=CR(I, Br), >C=CRCl, RCH_2CH_2Cl. Secondary halides are much less suited to coupling with lithium di-*n*-butylcopper than are primary halides. For example, reaction of this copper reagent with cyclohexyl iodide either in ether or tetrahydrofuran gave no detectable *n*-butylcyclohexane but mainly cyclohexene.

It should be noted that *n*-butyllithium (or ethyllithium) is a totally unsatisfactory reagent for most of the transformations discussed above, since it exhibits a much greater tendency to cause proton abstraction leading to 1,2 elimination and metal–halogen exchange.[10] It should also be pointed out that the copper reagents allow the use of substrates containing functional groups such as COOH and $CONR_2$ in unprotected form (see eq 9 and 10) and also can lead to stereospecific coupling processes (see eq 4 and 5). This latter property of the cross-coupling reaction has been used effectively in stereospecific syntheses of farnesol[11] and insect juvenile hormone.[12]

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(9) Significant solvent effects have been noted. Whereas in ether as solvent benzyl bromide reacts with lithium di-*n*-butylcopper to give mainly 1,2-diphenylethane (*ca.* 60%) and lesser amounts of *n*-amylbenzene (30%), in tetrahydrofuran these products are generated in yields of 60 and 10%, respectively. On the other hand, the yields of cross-coupling product from the reaction of lithium di-*n*-butylcopper with some halides, *e.g.*, certain vinylic bromides, are higher when ether or a hydrocarbon rather than tetrahydrofuran is used as solvent. The reactions of lithium di-*n*-butylcopper have been observed to proceed more rapidly in tetrahydrofuran than in ether.

(10) See, for example, H. Gilman and R. G. Jones, *J. Am. Chem. Soc.*, **63**, 1441 (1941); H. Gilman, W. Langham, and F. W. Moore, *ibid.*, **62**, 2327 (1940); D. E. Applequist and D. F. O'Brien, *ibid.*, **85**, 743 (1963).

(11) E. J. Corey, J. A. Katzenellenbogen, and G. H. Posner, *ibid.*, **89**, 4245 (1967).

(12) E. J. Corey, J. A. Katzenellenbogen, N. W Gilman, S. A. Roman, and B. W. Erickson, *ibid.*, **90**, 5618 (1968).

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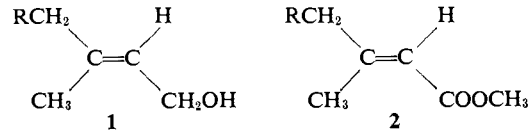
New Methods for the Oxidation of Aldehydes to Carboxylic Acids and Esters

Sir:

In connection with a synthesis of insect juvenile hormone which has been under study in these laboratories,[1] it was desirable to devise a simple method for the stereospecific conversion **1** → **2** under mild condi-



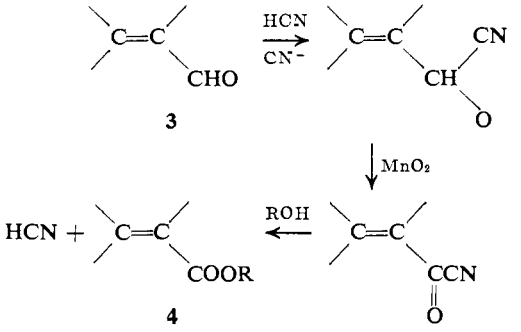
tions. This communication describes an efficient and useful oxidation process *via* aldehyde intermediates which has been developed for this purpose and another method which permits the oxidation of aldehydes to carboxylic acids in neutral or slightly basic media.

Manganese dioxide (active[2]) is an effective and selective oxidizing agent which cleanly converts primary allylic alcohols to conjugated aldehydes[3a] without sig-

(1) E. J. Corey, J. A. Katzenellenbogen, N. W. Gilman, S. Roman, and B. W. Erickson, *J. Am. Chem. Soc.*, 90, 5618 (1968).

(2) (a) S. Ball, T. W. Goodwin, and R. A. Morton, *Biochem. J.*, **42**, 516 (1948); (b) 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).

nificant further oxidation to carboxylic acids. It was anticipated, however, that in the presence of HCN and CN^- a conjugated aldehyde would be converted to the cyanohydrin which should be susceptible to further oxidation by manganese dioxide to an acyl cyanide leading finally in an alcoholic medium to an ester; this is represented by the sequence **3** → **4**. Such a process has now been demonstrated for the following aldehydes which were converted to the corresponding carboxylic methyl esters in the yields indicated: benzaldehyde (>95%), cinnamaldehyde (>95%), furfural



(>95%), geranial (85–95%), and farnesal (95%). In order to confirm the behavior of the intermediates shown in the scheme **3** → **4**, the cyanohydrin of cinnamaldehyde[4] was treated with manganese dioxide and sodium cyanide in methanol. Methyl cinnamate was obtained in high yield as expected on the basis of the sequence **3** → **4**.

The oxidation of geraniol *via* geranial to methyl geranate is illustrative of the experimental procedure.

A mixture of 50 mg of geraniol and 575 mg of active manganese dioxide[2b] in 8 ml of hexane was stirred at 0° for 30 min. Filtration and removal of solvent afforded 48 mg of geranial shown by nmr and infrared analysis to be >95% pure and also free of neral (the α,β-geometrical isomer). The geranial so obtained was stirred with a mixture of 82 mg of sodium cyanide, 30 mg of acetic acid, and 575 mg of manganese dioxide in methanol for 12 hr at 20–25° to give after removal of methanol, partitioning between ether and water, and concentration of the ether extract 51 mg of methyl geranate, spectroscopically (infrared, nmr) identical with an authentic sample and having >99% purity by gas chromatographic (gc) analysis.

Although the simplicity and convenience of this oxidation procedure are appealing, the fact that the reaction proceeds in high yield without *cis–trans* isomerization of the α,β-olefinic linkage is even more important. The traditional method of oxidation of an aldehyde to carboxylic acid using alkaline silver(I) oxide (Ag_2O)[3b] is relatively unsatisfactory for α,β-unsaturated aldehydes, since appreciable *cis–trans* α,β isomerization and other base-catalyzed side reactions can occur. The highly successful application of the the new cyanide-catalyzed oxidative esterification to the synthesis of insect juvenile hormone[1] illustrates the practical utility of this method.

Nonconjugated aldehydes are not converted to esters by the action of cyanide ion and manganese dioxide in methanol, despite the fact that cyanohydrin formation occurs even more readily in these cases than with conjugated aldehydes. We were therefore led to try the more powerful argentic oxide[5] as the oxidizing reagent in place of manganese dioxide. Surprisingly, reaction of cinnamaldehyde with argentic oxide (10 equiv) and sodium cyanide (5 equiv) in methanol at 25° for 2 hr led to *cinnamic acid* (>90% yield) and *not* the methyl ester. The cyanohydrin of cinnamaldehyde,[4] when treated with argentic oxide (dried at 50° (0.1 mm)) and sodium or potassium cyanide in reagent methanol (containing 0.05% water), also afforded cinnamic acid and no methyl cinnamate. In addition, benzaldehyde was converted to benzoic acid and not methyl benzoate by the action of argentic oxide (10 equiv) and sodium cyanide (5 equiv) after 6 hr in dry methanol, and the nonconjugated aldehyde 3-cyclohexenylcarboxaldehyde was smoothly transformed into 3-cyclohexenylcarboxylic acid under these conditions. Thus, the cyanide-catalyzed[6] oxidation of aldehydes in methanol can be directed to give either methyl ester (with active MnO_2) or carboxylic acid (with AgO). The difference between these systems may be due to the presence of nucleophilic hydroxide or oxide ions as highly reactive species on the surface of argentic oxide, which strongly catalyze heterogeneous hydrolysis of the acyl cyanide in this system, and the absence of such effects with the manganese dioxide reagent.

An even simpler conversion of aldehydes to carboxylic acids which is especially applicable to nonconjugated aldehydes has been effected by means of argentic oxide in tetrahydrofuran–water (9:1) at 25° under neutral conditions. Using a molar ratio of oxide to aldehyde of 4:1 and reaction times of 14 hr, dodecanal and 3-cyclohexenylcarboxaldehyde, for example, were oxidized to the corresponding acids in 90 and 97% yields, respectively. The oxidation of conjugated aldehydes under these conditions is considerably slower, and so the cyanide-catalyzed oxidation is preferable in such cases.

This work is being continued.[7]

Acknowledgment. We are indebted to the National Science Foundation and the National Institutes of Health for financial support.

(3) See L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," John Wiley & Sons, Inc., New York, N. Y., 1967: (a) pp 637–643; (b) pp 1012–1013.

(4) F. Nerdel and H. Rachel, *Ber.*, **89**, 671 (1956).

(5) (a) In an unpublished study in these laboratories by Dr. P. A. Vatakencherry (1961), it has been shown that argentic oxide [prepared by the method of A. A. Noyes, D. De Vault, C. D. Coryell, and T. J. Deahl, *J. Am. Chem. Soc.*, **59**, 1326 (1937)] oxidizes nonconjugated secondary alcohols such as cyclopentanol and cyclohexanol to ketones at reflux in chloroform or benzene more rapidly than does manganese dioxide; (b) the argentic oxide used in this work was conveniently prepared by the method of F. Jirsa [*Z. Anorg. Allgem. Chem.*, **225**, 302 (1935)] which involves addition of potassium hydroxide to a solution of potassium permanganate and silver nitrate in water. The precipitate of AgO was washed exhaustively with water until the washings were free of permanganate and base; (c) for other studies of AgO as an oxidizing agent see J. B. Lee and T. G. Clarke, *Tetrahedron Letters*, 415 (1967), and L. Syper, *ibid.*, 4193 (1967).

(6) The catalytic effect of cyanide ion on the AgO oxidation of cinnamaldehyde in methanol was also indicated by the following observations: (1) little, if any, oxidation to cinnamic acid occurred in the absence of cyanide, (2) addition of bases such as sodium acetate, potassium bicarbonate, or potassium carbonate in place of cyanide led at most to a relatively modest degree of oxidation to the acid.

(7) Subsequent to the preparation of this manuscript a publication appeared describing a comparative study of the oxidation of aldehydes to acids in aqueous base with Ag_2O and AgO as reagents; see S. C. Thomason and D. G. Kubler, *J. Chem. Educ.*, **45**, 546 (1968).

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