

Efficient Methods for Oxidation of Alcohols

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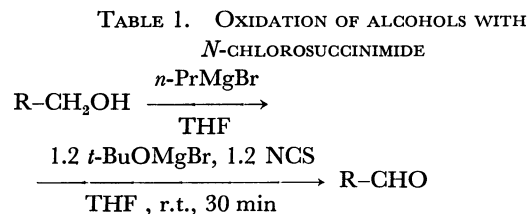
Treatment of alkoxy magnesium bromides, prepared *in situ* from alcohols and Grignard reagent, with *N*-chlorosuccinimide, *m*-chloroperbenzoic acid, or (diacetoxyiodo)benzene in the presence of *t*-butoxymagnesium bromide afforded the corresponding carbonyl compounds in good yields. A wide variety of alcohols, after being converted into their bromomagnesium salts by treatment with propylmagnesium bromide, were also selectively oxidized with 1,1'-(azodicarbonyl)dipiperidine to afford the corresponding ketones or aldehydes in excellent yields.

In the preceding communications, convenient methods were reported for the oxidation of alcohols to the corresponding ketones or aldehydes by the treatment of trialkyltin methoxide¹⁾ or bis(tributyltin) oxide,²⁾ and by that of alkoxy magnesium bromides with *N*-chlorosuccinimide in the presence of lithium *t*-butoxide.³⁾

These reactions were successfully applied to the oxidation of alcohols such as secondary alcohols, allylic alcohols, and benzylic alcohols, but not aliphatic and olefinic primary alcohols. Improvement of the methods was undertaken in order to establish an effective method for the oxidation of a wide variety of alcohols, especially aliphatic and olefinic primary alcohols.

In the previous methods, effective acid captors such as lithium *t*-butoxide, trialkyltin methoxide and bis(tributyltin) oxide were employed in order to scavenge hydrogen halides generated during the course of the reactions. It was found that the yields of the products depend a great deal on the kinds of acid captor. The effects of the other acid captors were reexamined in detail. The yields of the carbonyl compounds increased remarkably when *t*-butoxymagnesium bromide was used as an acid captor instead of lithium *t*-butoxide in the reaction of alkoxy magnesium bromide with *N*-chlorosuccinimide, the carbonyl compounds being obtained in the best yields when the molar ratio of alkoxy magnesium bromide, *t*-butoxymagnesium bromide, and *N*-chlorosuccinimide was 1:1.2:1.2. When several aliphatic primary alcohols, after being converted into the bromomagnesium salts by propylmagnesium bromide, were treated with a 1.2 molar amount of *N*-chlorosuccinimide in the presence of a 1.2 molar amount of *t*-butoxymagnesium bromide in tetrahydrofuran for 30 min at room temperature, the corresponding aldehyde were produced in good yields (Table 1). In the case of the oxidation of olefinic primary alcohol such as 7-phenyl-4-hepten-1-ol, the desired 7-phenyl-4-heptenal was obtained in low yield (34%), some by-products being produced.

In order to find suitable oxidizing reagents for the oxidation of olefinic primary alcohols, several oxidizing reagents were examined. It was found that when *m*-chloroperbenzoic acid or (diacetoxyiodo)benzene is used for the oxidation of the bromomagnesium salt of 7-phenyl-4-hepten-1-ol in the presence of *t*-butoxy-

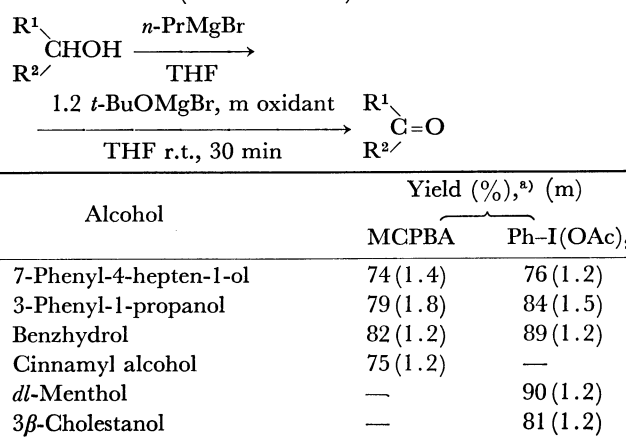


| Alcohol | Yield (%) |
|------------------------|------------------|
| 1-Octanol | 80 ^{a)} |
| 1-Heptanol | 77 ^{a)} |
| 3-Phenyl-1-propanol | 81 ^{b)} |
| 7-Phenyl-4-hepten-1-ol | 34 ^{b)} |

a) Yield determined by GLC. b) Isolated yield.

magnesium bromide, 7-phenyl-4-heptenal is obtained in fairly good yields. The bromomagnesium salt of 7-phenyl-4-hepten-1-ol, prepared from the alcohol and propylmagnesium bromide, was treated with a 1.2 molar amount of (diacetoxyiodo)benzene or *m*-chloroperbenzoic acid in the presence of a 1.2 molar amount of *t*-butoxymagnesium bromide in tetrahydrofuran for 30 min at room temperature. The desired 7-phenyl-4-heptenal was isolated in 76 and 74% yields, respectively. In a similar way, several kinds of alcohols such as aliphatic primary alcohol, secondary alcohol, benzylic alcohol, and allylic alcohol were oxidized to the corresponding carbonyl compounds in good yields by use of these reagents (Table 2). The yields of the oxidation

TABLE 2. OXIDATION OF ALCOHOLS WITH
m-CHLOROPERBENZOIC ACID OR
 (DIACETOXYIODO)BENZENE



| Alcohol | Yield (%), ^{a)} (m) | |
|------------------------|------------------------------|------------------------|
| | MCPBA | Ph-I(OAc) ₂ |
| 7-Phenyl-4-hepten-1-ol | 74 (1.4) | 76 (1.2) |
| 3-Phenyl-1-propanol | 79 (1.8) | 84 (1.5) |
| Benzhydrol | 82 (1.2) | 89 (1.2) |
| Cinnamyl alcohol | 75 (1.2) | — |
| <i>dl</i> -Menthol | — | 90 (1.2) |
| 3 β -Cholestanol | — | 81 (1.2) |

a) Isolated yield.

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product of the olefinic primary alcohol, 7-phenyl-4-hepten-1-ol, were not so good in comparison with those of the other kinds of alcohols, small amounts of by-products being obtained.

Further examination of suitable oxidizing reagents for the oxidation of olefinic primary alcohol was carried out. Concerning the oxidation of alcohols, an efficient method for ketone synthesis was reported.⁴⁾ That is, *s*-alkoxymagnesium bromides were prepared by the reaction of aldehydes with Grignard reagents followed by treatment with diethyl azodicarboxylate or 1,1'-(azodicarbonyl)dipiperidine, resulting in the formation of the corresponding ketones in good yields. Generally these azo compounds are inactive to olefinic linkage, and the use of azo compounds is expected to suppress the side reactions with respect to olefinic linkage of the alcohol. The oxidation of 7-phenyl-4-hepten-1-ol was attempted first by employing diethyl azodicarboxylate as an oxidant. However, the desired oxidation could not be observed and only an ester-exchanging reaction took place to give ethyl 7-phenyl-4-heptenyl azodicarboxylate and bis(7-phenyl-4-heptenyl)azodicarboxylate. To avoid this side reaction, dibenzoyldiimide was used as an oxidizing reagent instead of diethyl azodicarboxylate. The desired 7-phenyl-4-heptenal was obtained in only 20% yield, a by-product, 7-phenyl-4-heptenyl benzoate, being isolated in 38% yield accompanied by the cleavage of carbon-nitrogen bond of dibenzoyldiimide.

On the other hand, when 7-phenyl-4-hepten-1-ol was allowed to react with a 1.2 molar amount of propylmagnesium bromide in tetrahydrofuran and then treated with a 1.2 molar amount of 1,1'-(azodicarbonyl)dipiperidine at room temperature for 2 h, the desired 7-phenyl-4-heptenal was obtained in 89% yield along with 1,1'-(hydrazodicarbonyl)dipiperidine in 93% yield, 7% of 7-phenyl-4-hepten-1-ol being recovered after the separation by column chromatography (silica gel) (Table 3).

TABLE 3. OXIDATION OF 7-PHENYL-4-HEPTEN-1-OL WITH SEVERAL AZO COMPOUNDS

| R | Isolated yield (%) |
|------|--------------------|
| -OEt | 0 |
| -OPh | 20 |
| -N | 89 |

Similarly, the oxidation of various kinds of alcohols with 1,1'-(azodicarbonyl)dipiperidine afforded the corresponding ketones and aldehydes in excellent yields (89–99%). The results are summarized in Table 4.

An alternative method was adopted for the oxidation of alcohols having the carbonyl group for prevention of the addition reaction of the Grignard reagent to the

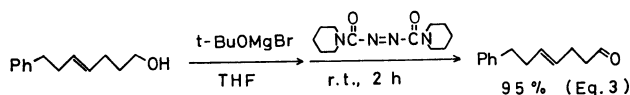
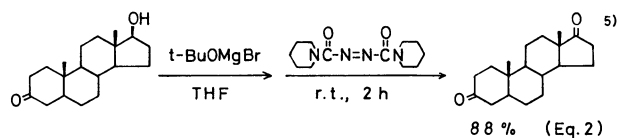
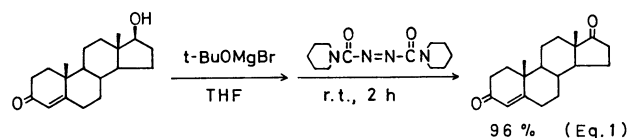
TABLE 4. OXIDATION OF VARIOUS ALCOHOLS WITH 1,1'-(AZODICARBONYL)DIPERIDINE

| Alcohol | Time | Yield (%) ^{a)} |
|------------------------|------------|-------------------------|
| 7-Phenyl-4-hepten-1-ol | 2 h | 89 |
| Cinnamyl alcohol | 2 h | 92 |
| Geraniol | 2 h | 96 |
| Benzhydrol | 2 h | 99 |
| 2-Phenyl-1-butanol | 2 h | 90 |
| 2-Octanol | over night | 91 ^{b)} |
| 3 β -Cholestanol | over night | 93 |
| Citronellol | 2 h | 89 |

a) Isolated yield. b) Yield determined by GLC.

carbonyl group. When *t*-butoxymagnesium bromide was employed in place of the Grignard reagent for the conversion of testosterone into the bromomagnesium salt, the oxidation of testosterone proceeded successfully, 4-androsten-3,17-dione being obtained in 96% yield (Eq. 1).

Similarly, stanolone and 7-phenyl-4-hepten-1-ol were oxidized to give the corresponding carbonyl compounds in excellent yields (Eqs. 2, 3).



Azo compounds such as diethyl azodicarboxylate⁶⁾ and 4-phenyl-1,2,4-triazoline-3,5-dione⁷⁾ react with free alcohols to afford the corresponding carbonyl compounds, but the yields are not so good. A long reaction time and elevated temperature are required for the oxidation with diethyl azodicarboxylate. 4-Phenyl-1,2,4-triazoline-3,5-dione is very unstable. Contrary to these results, the oxidation of alcohols proceeded under mild conditions (room temperature) by use of alkoxy-magnesium bromide in place of free alcohol, the corresponding carbonyl compounds being obtained in excellent yields. Use of 1,1'-(azodicarbonyl)dipiperidine instead of *N*-chlorosuccinimide, *m*-chloroperbenzoic acid and (diacetoxyiodo)benzene makes it possible to oxidize various kinds of alcohols selectively to the corresponding

carbonyl compounds without addition of acid captors such as lithium *t*-butoxide and *t*-butoxymagnesium bromide.

In general, reagents such as CrO₃-pyridine complex,⁸⁾ CrO₃-acetone,⁹⁾ dimethyl sulfoxide-dicyclohexylcarbodiimide,¹⁰⁾ dimethyl sulfide-*N*-chlorosuccinimide or chlorine¹¹⁾ are widely employed for the oxidation of alcohols to the corresponding ketones or aldehydes. However, some of them are very toxic [Cr(VI)], causing side reactions such as further oxidation of produced aldehydes and the formation of alkyl chlorides and sulfides. We have confirmed that a wide variety of alcohols are oxidized selectively to the corresponding ketones or aldehydes in excellent yields by the present procedure utilizing alkoxy magnesium bromides and 1,1'-(azodicarbonyl)dipiperidine.

Experimental

Materials. Commercial *N*-chlorosuccinimide was recrystallized quickly from hot water before use. The purity was determined by iodometry (purity >98%). *m*-Chloroperbenzoic acid was prepared by the reaction of *m*-chlorobenzoyl chloride with aqueous hydrogen peroxide and purified by washing with a phosphate buffer of pH 7.5 according to the procedure given in literature.¹²⁾ The purity was determined by iodometry (purity >97.5%). (Diacetoxyiodo)benzene was synthesized by the reaction of iodobenzene with peracetic acid,¹³⁾ the purity being determined in a similar way (purity >97%). 1,1'-(Azodicarbonyl)dipiperidine was prepared by the reaction of diethyl azodicarboxylate with piperidine,¹⁴⁾ and purified by recrystallization from a mixture of benzene and hexane (mp 134–135 °C). 7-Phenyl-4-heptene-1-ol was synthesized from dihydrofuran and 2-phenylethylmagnesium bromide according to the procedure of Brandron *et al.*¹⁵⁾ and purified by distillation (bp 119–120 °C/1.0 mmHg).

General Procedure of Oxidation of Alkoxy Magnesium Bromide with *N*-Chlorosuccinimide. To a solution of propylmagnesium bromide in dry THF (3 ml) prepared from magnesium (58 mg, 2.4 mmol) and propyl bromide (320 mg, 2.6 mmol) was added dropwise a solution of alcohol (1.0 mmol) and *t*-butyl alcohol (89 mg, 1.2 mmol) in THF (4 ml) at room temperature under argon atmosphere. After the reaction mixture had been stirred for 10 min, *N*-chlorosuccinimide (160 mg, 1.2 mmol) was added all at once at room temperature. The reaction mixture was stirred for 30 min, quenched by the addition of brine and solid Na₂S₂O₃·5H₂O, and extracted with diethyl ether. The ether layer was washed with saturated aqueous NaHCO₃ and brine, and dried over anhydrous Na₂SO₄. The yield of the corresponding aldehyde was determined by vapor phase chromatography or isolation using preparative thin layer chromatography (silica gel).

General Procedure of Oxidation of Alcohols with *m*-Chloroperbenzoic Acid. A solution of propylmagnesium bromide (1.2 mmol) in THF (3 ml) was prepared in a similar way and treated with a THF (4 ml) solution of an alcohol (1 mmol) and *t*-butyl alcohol (89 mg, 1.2 mmol) at room temperature under argon atmosphere, and stirred for 10–15 min at room temperature. This solution was then treated with crystalline *m*-chloroperbenzoic acid (1.2–1.8 mmol) at room temperature, stirred for 30 min at room temperature, and quenched by the addition of brine and solid Na₂S₂O₃·5H₂O. Benzene was added to the mixture and the resulting precipitate was filtered off. The organic layer was washed with saturated aqueous NaHCO₃ and brine, and dried over anhydrous Na₂SO₄.

After removal of the solvent, the corresponding carbonyl compound was isolated by preparative thin layer chromatography (silica gel).

General Procedure of Oxidation of Alcohols with (Diacetoxyiodo)benzene. A solution of alkoxy magnesium bromide (1 mmol) and *t*-butoxymagnesium bromide (1.2 mmol) in THF (7 ml) was prepared in a similar way, treated with crystalline (diacetoxyiodo)benzene (1.2–1.5 mmol) at room temperature. After being stirred for 30 min at room temperature, the mixture was quenched by addition of brine and solid Na₂S₂O₃·5H₂O, and extracted with ethyl acetate. The organic layer was washed with saturated aqueous NaHCO₃ and brine, and dried over anhydrous Na₂SO₄. After removal of the solvent, the yield was determined by isolation using preparative thin layer chromatography (silica gel) or column chromatography (silica gel).

Oxidation of 7-Phenyl-4-hepten-1-ol with (Diacetoxyiodo)benzene.

A THF (3 ml) solution of propylmagnesium bromide was prepared from magnesium (58 mg, 2.4 mmol) and propyl bromide (320 mg, 2.6 mmol), then treated with a THF (4 ml) solution of 7-phenyl-4-hepten-1-ol (186 mg, 0.98 mmol) and *t*-butyl alcohol (89 mg, 1.2 mmol) at room temperature under argon atmosphere. The reaction mixture was stirred for 10 min at room temperature, a THF (10 ml) solution of (diacetoxyiodo)benzene (429 mg, 1.33 mmol) being added dropwise within the period of 20 min. The mixture was stirred for additional 30 min. After the usual work-up, 7-phenyl-4-heptenal (140 mg, 76%) was isolated by column chromatography (silica gel).

NMR (CCl₄) δ 2.12–2.80 (m, 8H), 5.32–5.55 (m, 2H), 7.15 (s, 5H), 9.70 (s, 1H); IR 1725 cm⁻¹.

2,4-dinitrophenylhydrazone, mp 96.0–96.2 °C. Found: C, 61.94; H, 5.38; N, 15.02%. Calcd for C₁₉H₂₀N₄O₄: C, 61.94; H, 5.47; N, 15.21%.

Oxidation of 7-Phenyl-4-hepten-1-ol with 1,1'-(Azodicarbonyl)dipiperidine Utilizing Propylmagnesium Bromide.

To a THF (3 ml) solution of propylmagnesium bromide (160 mg, 1.3 mmol) was added dropwise a THF (2 ml) solution of 7-phenyl-4-hepten-1-ol (190 mg, 1.0 mmol) at room temperature under argon atmosphere. A THF (4 ml) solution of 1,1'-(azodicarbonyl)dipiperidine (320 mg, 1.2 mmol) was then added dropwise to the mixture. The mixture was stirred for 2 h at room temperature, quenched by addition of brine, and extracted with ethyl acetate. The organic layer was washed with saturated aqueous NaHCO₃ and brine, and dried over anhydrous Na₂SO₄. After removal of the solvent, the residue was separated by column chromatography (silica gel). Elution with benzene, methylene chloride, and methanol afforded the desired 7-phenyl-4-heptenal (167 mg, 89%), 7-phenyl-4-hepten-1-ol (13 mg, 7%) and 1,1'-(hydrazodicarbonyl)dipiperidine (234 mg, 92%), respectively.

General Procedure of Oxidation of Alcohols with 1,1'-(Azodicarbonyl)dipiperidine Utilizing Propylmagnesium Bromide.

To a solution of propylmagnesium bromide in THF (3 ml) prepared from magnesium (29 mg, 1.2 mmol) and propyl bromide (160 mg, 1.3 mmol) was added dropwise a THF (2 ml) solution of an alcohol (1 mmol) at room temperature under argon atmosphere. A THF (4 ml) solution of 1,1'-(azodicarbonyl)dipiperidine was then added dropwise at room temperature. The mixture was stirred for 2 h—overnight, quenched by addition of brine, and extracted with ether. After filtration of the precipitate, the organic layer was washed with saturated aqueous NaHCO₃ and brine, and dried over anhydrous Na₂SO₄. The yield of the corresponding ketone or aldehyde was determined by isolation using column chromatography (silica gel) or by vapor phase chromatography analysis.

Oxidation of Testosterone with 1,1'-(Azodicarbonyl)dipiperidine

Utilizing t-Butoxymagnesium Bromide. To a THF (3 ml) solution of propylmagnesium bromide prepared from magnesium (29 mg, 1.2 mmol) and propyl bromide (160 mg, 1.3 mmol) was added dropwise a THF (2 ml) solution of *t*-butyl alcohol (89 mg, 1.2 mmol). A THF (2 ml) solution of testosterone (388 mg, 1.0 mmol) was then added, and the mixture was treated with a THF (4 ml) solution 1,1'-(azodicarbonyl)-dipiperidine (302 mg, 1.2 mmol). After the usual work-up, the desired 4-androsten-3,17-dione (374 mg, 96%) was isolated by preparative thin layer chromatography (silica gel).

NMR(CDCl₃) δ 0.93 (s, 3H), 1.23 (s, 3H), 5.72 (s, 1H); IR 1660, 1740 cm⁻¹, mp 170–171 °C (lit, 169–170 °C¹⁰) Found: C, 79.42; H, 9.30%. Calcd for C₁₉H₂₈O₂: C, 79.68; H, 9.15%.

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