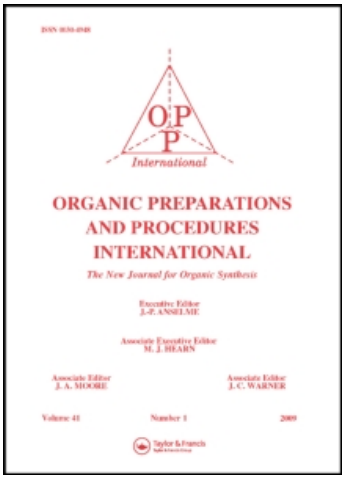

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A VERSATILE METHOD FOR THE CONVERSION OF KETONES TO ALDEHYDES

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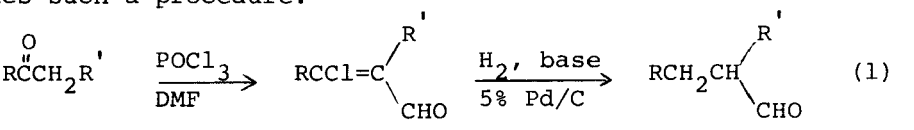
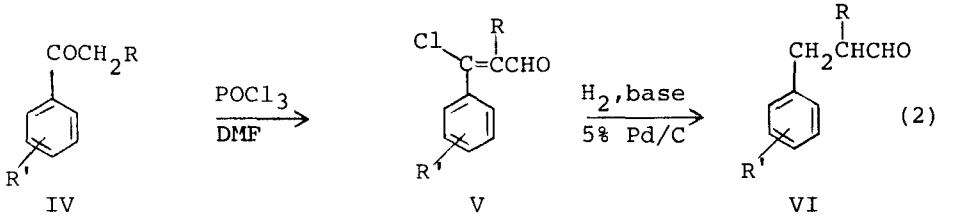
A variety of ketones I are readily accessible by standard organic reactions. We were interested in a convenient, economical method for the transformation of these ketones to aldehydes.[1] The synthetic transformation described in Eq. 1 outlines such a procedure.



I II III (1)

The formation of β-chloro-α,β-unsaturated aldehydes II from ketones has been described by a number of authors.[2,3] The structure of the β-chloro-α,β-unsaturated aldehydes from both symmetrical and unsymmetrical ketones can be easily predicted. The Vilsmeier reagent attacks the more thermodynamically stable enol form of the ketone to yield a β-keto aldehyde. This β-keto aldehyde is further transformed by the Vilsmeier reagent to a β-chloro-α,β-unsaturated aldehyde. Thus, the combination of the two steps of formation of β-chloro-α,β-unsaturated aldehydes II followed by hydrogenation constitutes an extremely useful method for the transformation of ketones of type I to aldehydes of structural type III.

A variety of propiophenones IV (R = methyl) were readily synthesized in excellent yields by the Friedel-Crafts reaction. These propiophenones, when reacted with the Vilsmeier reagent, gave excellent yields of the β-chlorocinnamaldehydes (Table 1). The reaction was found to be insensitive to substituents in the aromatic ring. In the first two examples of Table 1 the yields were maximized and nearly quantitative yields of β-chlorocinnamaldehyde V can be obtained. The β-chlorocinnamaldehydes V were found to be extremely stable to hydrolysis. The chloro group could be displaced by the sodium salt of ethyl mercaptan, but was unaffected by a refluxing solution of 30% potassium or sodium hydroxide. This inertness



(2)

a) R = CH_3, R' = 4-t-Butyl b) R = CH_3, R' = 4-Isopropyl

c) R = CH_3, R' = 2,4-Dimethyl d) R = CH_3, R' = 2,4,5-Trimethyl

e) R = CH_3, R' = 4-Methoxy f) R = CH_3, R' = 4-n-Heptyl

g) R = CH_3, R' = 4-CH_3 h) R = CH_3, R' = 4-Ethyl

i) R = n-Octyl, R' = Hydrogen

of the chloro group was advantageous in that 30% potassium hydroxide could be used as a base during hydrogenation of V to VI without adverse side-reactions. The hydrogenations proceeded in good yields and provided an economical synthesis of several important fragrance chemicals,[4] such as Lilial®[5] (VIa, R' = t-butyl and R = methyl) and cyclamen aldehyde (VIb, R' =

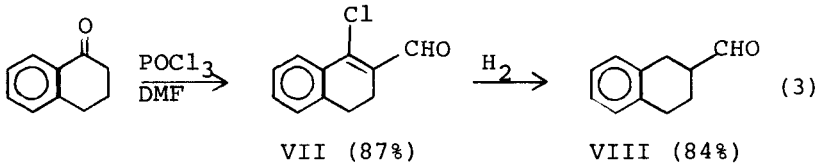
isopropyl and R = methyl).

TABLE 1. Yields of V and VI from IV

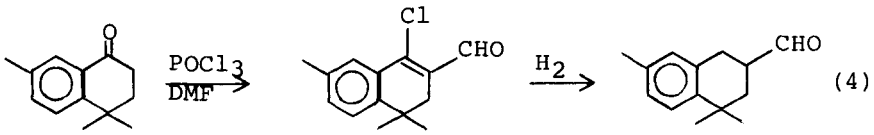
Compound	Yield (%)	Compound	Yield (%)
Va	96[a]	VIa	88[a]
Vb	96[a]	VIb	82[a]
Vc	87	VIc	80
Vd	83	VId	75
Ve	86	VIe	74
Vf	92	VIf	70
Vg	88	VIg	75
Vh	86	VIh	66
Vi	74	VIi	86

a) Yields were maximized

β-Tetrahydronaphthalene carboxaldehydes VIII and X were readily synthesized from α-tetralones (Eqs. 3 and 4).

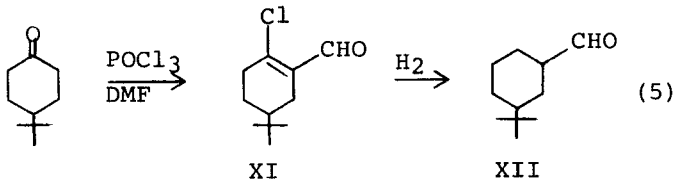


VII (87%) VIII (84%) (3)



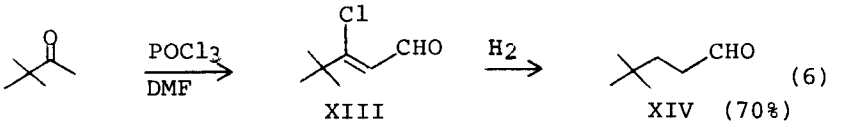
IX (89%) X (81%) (4)

3-t-Butylcyclohexane carboxaldehyde was obtained in 32% yield from readily available 4-t-butylcyclohexanone. Since crude chloroaldehyde XI decomposed on attempted distillations, it was hydrogenated directly.



XI XII (5)

A number of β-chloro substituted acroleins from dialkyl ketones such as acetone, ethyl methyl ketone and pinocolone have been described previously.[3] These β-substituted acroleins can also be hydrogenated to saturated aldehydes (e.g. XIII ⟶ XIV).



XIII XIV (70%) (6)

In summary, this process for the conversion of ketones to aldehydes has the superior attributes of high yields, ease of operation, attractive economics and as a method to obtain aldehydes which are not readily accessible.

While this work was in progress, a reduction of several other β-chloro-α,β-unsaturated aldehydes to α,β-unsaturated aldehydes was also reported.[9]

EXPERIMENTAL

Boiling points are uncorrected. NMR spectra were obtained on a Varian A-60 instrument. The elemental analyses were carried out by Instranal Laboratories, Rensselaer, New York. The ketones were readily available or easily prepared by the Friedel-Crafts reaction between the appropriate substituted benzene and acid chloride.

Standard Procedures

Aromatic Chloro Aldehydes. - Phosphorus oxychloride (462 g)

was added to 400 g of dimethylformamide (DMF) at such a rate as to maintain the temperature below 25° by ice bath cooling. After stirring for 0.5 hr., the ketone (1 mole) was added dropwise to the mixture at 70-80°. The solution was heated at 70-80° for 5 hrs. The reaction was cooled and 720 g of 30% sodium hydroxide solution was added and the temperature was maintained below 70° by ice bath cooling. The solution was stirred at 60-70° for 0.5 hr. Water (500 g) was added and the mixture extracted with 3 x 400 ml of ethylene dichloride. The combined extracts were dried ($MgSO_4$), filtered, concentrated and distilled.

Hydrogenations. - The chloroaldehyde (0.30 mole), 1.0 g of 5% Pd/C, base (either 0.30 mole of a 30% sodium hydroxide solution or 0.30 mole of K_2CO_3), 40 g of water and 32 g of methanol were placed in a Parr apparatus and hydrogenated at 20-50 psi and 50-60°C until the theoretical amount of hydrogen had been absorbed (about 3.5 hrs.). The progress of the hydrogenation was monitored by gas chromatography on a 10% Carbowax column (6 ft). The chloroaldehyde, unsaturated aldehyde, saturated aldehyde and any saturated alcohol are easily distinguished. The solution was filtered and the aqueous phase extracted with 100 g of ethylene dichloride. The solution was dried ($MgSO_4$), filtered, concentrated on a rotary evaporator and distilled. The reported yields represent material of greater than 98% purity. (Trace amounts of saturated alcohol may be present). All dihydrocinnamaldehydes were identical by GC, NMR, and IR to authentic samples.[1,10]

4-t-Butyl-β-chloro-α-methylcinnamaldehyde (Va).- The standard procedure using 190 g of 4-t-butylpropiophenone yielded 227.2g (96% of product, bp. 122°/1.0 mm. NMR ($CDCl_3$): δ 9.55 (s, 1), 7.4 (s, br, 4), 2.08 (s, br, 3), 1.33 (s, 9).

Anal. Calcd for $C_{14}H_{17}ClO$: C, 71.02; H, 7.22; Cl, 15.00.
Found: C, 71.04; H, 7.52; Cl, 14.78.

β-Chloro-4-isopropyl-α-methylcinnamaldehyde (Vb).- 4-Isopropylpropiophenone (176.2 g) was reacted in the same manner to yield 213.6 g (96%) of the desired product, bp. 114°/1.0 mm. NMR ($CDCl_3$): δ 9.50 (s, 1), 7.32 (s, br, 4), 3.08 (m, 1), 2.05 (s, 3) and 1.30 (d, 6).

Anal. Calcd for $C_{13}H_{15}ClO$: C, 70.09; H, 6.78; Cl, 15.94.
Found: C, 70.26; H, 6.86; Cl, 15.66.

β-Chloro-2,4-α-trimethylcinnamaldehyde (Vc).- 2,4-Dimethylpropiophenone (162.2 g) yielded 181.2 g (87%) of the desired product, bp. 110°/1.0 mm. NMR ($CDCl_3$): δ 9.46 (s, 1), 7.1 (s, br, 3), 2.35 (s, 3), 2.28 (s, 3) and 2.05 (s, 3).

Anal. Calcd for $C_{12}H_{13}ClO$: C, 69.06; H, 6.28; Cl, 16.99.
Found: C, 68.89; H, 6.43; Cl, 17.12.

β-Chloro-2,4,5-α-tetramethylcinnamaldehyde (Vd).- 2,4,5-Trimethylpropiophenone (176.2 g) yielded 185.2 g (83.2%) of the desired product, bp. 115°/1.3 mm. NMR ($CDCl_3$): δ 9.44 (s, 1), 7.0 (s, br, 2), 2.22 (s, br, 9) and 2.07 (s, 3).

Anal. Calcd for $C_{13}H_{15}ClO$: C, 70.10; H, 6.79; Cl, 15.92.
Found: C, 70.08; H, 6.71; Cl, 15.68

β-Chloro-4-methoxy-α-methylcinnamaldehyde (Ve).- 4-Methoxypropiophenone (164.2 g) yielded 180 g (86%) of the desired prod-

uct, bp. 130°/1.0 mm. NMR ($CDCl_3$): δ9.33 (s, 1), 7.3 and 6.9 (2d, 4), 3.79 (s, 3) and 2.04 (s, 3).

Anal. Calcd for $C_{11}H_{11}ClO_2$: C, 62.71; H, 5.26; Cl, 16.83.
Found: C, 62.62; H, 5.41; Cl, 17.07.

β-Chloro-4-n-heptyl-α-methylcinnamaldehyde (Vf).- 4-n-Heptylpropiophenone (232.4 g) yielded 255.2 g (91.5%) of the desired product, bp. 165°/1.2 mm. NMR ($CDCl_3$): δ 9.68 (s, 1), 7.27 (s, br, 4), 2.6 (m, 2), 2.05 (s, 3), 1.33 (m, 10) and 0.9 (d, 3).

β-Chloro-4,α-dimethylcinnamaldehyde (Vg).- 4-Methylpropiophenone (148.2 g) yielded 170.4 g (88%) of the desired product, bp. 98°/1.0 mm. NMR ($CDCl_3$): δ 9.52 (s, 1), 7.23 (s, br, 4), 2.37 (s, 3) and 2.04 (s, 3).

Anal. Calcd for $C_{11}H_{11}ClO$: C, 67.87; H, 5.70.
Found: C, 67.42; H, 5.93.

β-Chloro-4-ethyl-α-methylcinnamaldehyde (Vh).- 4-Ethylpropiophenone (162.2 g) yielded 180.4 g (86%) of the desired product, bp. 118°/1.3 mm. NMR ($CDCl_3$): δ 9.53 (s, 1), 7.26 (s, br, 4), 2.7 (q, 2), 2.05 (s, 3) and 1.24 (t, 3).

Anal. Calcd for $C_{12}H_{13}ClO$: C, 69.06; H, 6.28; Cl, 17.00.
Found: C, 69.22; H, 6.38; Cl, 17.42.

β-Chloro-α-octylcinnamaldehyde (Vi).- Decanophenone (116.2 g) was reacted to yield 103.2 g (74%) of the desired product, bp. 159°/1.3 mm. NMR ($CDCl_3$): δ 9.64 (s, br, 1), 7.39 (s, 5), 2.59 (m, 2), 1.34 (m, 12) and 0.89 (m, 3).

4-t-Butyl-α-methyldihydrocinnamaldehyde(VIa)[4].- Hydrogenation of Va gave a 88% yield of VIa, bp. 101°/1.0 mm. This material was

identical to Lilial.®

4-Isopropyl-α-methyldihydrocinnamaldehyde (VIb)[4].- Hydrogenation of Vb yielded 82% of VIb, bp. 120°/1.0 mm. This material was identical to the commercial product cyclamen aldehyde.

2,4-α-Trimethyldihydrocinnamaldehyde (VIc).- Hydrogenation of Vc yielded 80% of VIc, bp. 92°/1.0 mm. NMR ($CDCl_3$): δ 9.75 (s, br, 1), 7.0 (s, 3), 2.6-3.2 (m, 3), 2.24 (s, 6) and 1.0 (d, 3).

2,4,5-α-Tetramethyldihydrocinnamaldehyde (VId).- Hydrogenation of Vd gave 75% of VId, bp. 120°/1.0 mm. NMR ($CDCl_3$): δ 9.78 (s, br, 1), 6.9 (s, br, 2), 3.1-2.3 (m, 3), 2.16 (s, br, 9) and 1.1 (d, 3).

4-Methoxy-α-methyldihydrocinnamaldehyde (VIe).- Hydrogenation of Ve yielded 74% of VIe, bp. 118°/1.5 mm. NMR ($CDCl_3$): δ 9.70 (s, 1), 7.3 and 7.0 (2d, 4), 3.8 (s, 3), 3.1-2.4 (m, 3) and 1.1 (d, 3).

4-n-Heptyl-α-methyldihydrocinnamaldehyde (VIf).- Hydrogenation of Vf yielded 70% of VIf, bp. 158°/1.0 mm. NMR ($CDCl_3$): δ 9.9 (s, br, 1), 7.07 (s, 4), 3.0-2.4 (m, 5), 1.3 (m, 13) and 0.95 (d, 3).

4,α-Dimethyldihydrocinnamaldehyde (VIg).- Hydrogenation of Vg yielded 75% of VIg, bp. 60°/0.1 mm. NMR ($CDCl_3$): δ 9.68 (d,1), 7.01 (s, 4), 3.1-2.4 (m, 3), 2.26 (s, 3) and 1.00 (d, 3).

4-Ethyl-α-methyldihdyrocinnamaldehyde (VIh).- Hydrogenation of Vh yielded 66% of VIh, bp. 88°/1.0 mm. NMR ($CDCl_3$): δ 9.70 (d, 1), 7.04 (s, 4), 3.0-2.4 (m, 5), 1.20 (t, 3) and 1.10 (t, 3).

α-n-Octyldihydrocinnamaldehyde (VIi). - Hydrogenation of Vi yielded 86% of VIi, bp. 148°/1.0 mm. NMR ($CDCl_3$): δ 11.1 (s, br, 1), 7.19 (s, 5), 2.85 (m, 3), 1.25 (m, 13) and 0.88 (m, 3).

1-Chloro-3,4-dihydronaphthalene-2-carboxaldehyde (VII).- The standard procedure (with the modification that NaOAc was used instead of 30% sodium hydroxide) using 73.1 g of α-tetralone yielded 81.1 g (87%) of VII, bp. 122°/0.4 mm, lit.[6] bp. 145-153°/5 mm. NMR ($CDCl_3$): δ 10.33 (s, 1), 7.7 and 7.2 (m, 4), and 2.65 (m, 4).

1,2,3,4-Tetrahydro-2-naphthaldehyde (VIII).- Hydrogenation of 28.9 g of VII in presence of K_2CO_3 yielded 17.7 g (84%) of VIII, bp. 98°/1.0 mm. NMR ($CDCl_3$): δ 9.72 (s, br, 1), 7.1 (s, 4) and 3.1-1.6 (m, 7). Product described by Alder.[7]

1-Chloro-4,4,7-trimethyl-3,4-dihydronaphthalene-2-carboxaldehyde (IX).- The standard procedure (with the modification that NaOAc was used instead of 30% sodium hydroxide) using 18.8 g of 4,4,7-trimethyl-α-tetralone yielded 19.0 g (89%) of IX, bp. 143°/1.0 mm. NMR ($CDCl_3$): δ 10.45 (s, 1), 7.7 (s, br, 1), 7.28 (d, 2), 2.52 (s, 2), 2.38 (s, 3) and 1.22 (s, 6).

Anal. Calcd for $C_{14}H_{15}ClO$: C, 71.62; H, 6.43; Cl, 15.15.
Found: C, 71.67; H, 6.45; Cl, 15.18.

4,4,7-Trimethyl-1,2,3,4-tetrahydro-2-naphthaldehyde (X).- Hydrogenation of 12.1 g of IX, using 15.2 g of K_2CO_3 yielded 8.4 g (81%) of X, bp. 118°/1.0 mm. NMR ($CDCl_3$): δ 9.77 (s, br, 1), 7.1 (m, 3), 2.85 (m, 2), 2.35 (d, 2), 2.25 (s, 3), 1.9 (m, 1) and 1.23 (d, 6).

Anal. Calcd for $C_{14}H_{18}O$: C, 83.14; H, 8.95.
Found: C, 83.19; H, 8.71.

3-t-Butylcyclohexane carboxaldehyde (XII).- Phosphorus oxychloride (230 ml, 2.5 mol) was added dropwise to 400 g of dimethylformamide at such a rate as to maintain the temperature below 25° by ice bath cooling. After stirring for 0.5 hr, the reaction was warmed to 35° and 153 g of p-t-butylcyclohexanone was added dropwise over 1 hr at 35-40° (cooling necessary). The reaction was maintained at 50-60°C for 2 hrs. The reaction was cooled in an ice bath and 1,000 ml of saturated sodium acetate was added dropwise so that a temperature of less than 50° was maintained. After stirring at 50° for 30 min., 1,000 ml of water and 400 ml of ethylene dichloride was added. The ethylene dichloride was separated and the aqueous phase extracted with 2 x 200 ml of ethylene dichloride. The combined extracts were dried ($MgSO_4$), filtered and concentrated on a rotary evaporator (3 mm, bath temperature <60°C) to yield 241 g of crude chloroaldehyde (XI).

241 g of crude XI, 300 g of K_2CO_3, 250 ml of ethanol, 250 ml of water and 15 g of 5% Pd/C were hydrogenated at 20-50 psi until hydrogen ceased to be absorbed. The solution was filtered and 400 ml of ethylene dichloride added. The ethylene dichloride was dried ($MgSO_4$), filtered and concentrated on a rotary evaporator to yield 53.5 g XII, bp. 72°/0.5 mm (32% from p-t-butylcyclohexanone). NMR ($CDCl_3$): δ 9.83 (s) and 9.73 (br) (total 1), 2.6-1.4 (m, 10), and 0.97 (s, br, 9).

Anal. Calcd for $C_{11}H_{20}O$: C, 78.49; H, 12.00.
Found: C, 78.21; H, 11.78.

4,4-Dimethylpentanal (XIV).- 3-Chloro-4,4-dimethyl-2-pentenal[3] XIII (13.3 g), 0.10 mol), ethanol (50 ml), water (50 ml), K_2CO_3 (13.8 g, 0.10 mol) and 2.0 g of 5% Pd/C were hydrogenated on a Parr apparatus until the theoretical amount of hydrogen had been absorbed. The mixture was filtered and extracted with 2 x 50 ml of CH_2Cl_2. The extracts were dried ($MgSO_4$), filtered and concentrated on a rotary evaporator. Distillation yielded 8.0 g (70%) of 4,4-dimethylpentanal XIV, bp. 67°/80 mm, lit.[8] bp. 38-40/18 mm.

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