with that of the product of methylation of 4.

3-Acetamido-4-(benzylamino)-3-buten-2-one (24). 3 (142 mg, 1.0 mmol) was treated with benzylamine (118 mg, 1.2 mmol) in ethanol (10 mL) at reflux for 8 h. The cooled mixture was concentrated in vacuo and the residue recrystallized from ethyl acetate, giving 185 mg (80%) of fine white needles: mp 160–162 °C; mass spectrum, m/e (relative intensity) M^+, 232 (62.0), 215 (5.8), 189 (45.8), 147 (8.6), 99 (23.1), 91 (100), 72 (12.6), 43 (21.6); ^1H NMR (CD_3OD) δ 2.07 (3 H, s), 2.15 (3 H, br s), 4.48 (2 H, s), 7.3 (5 H, m), 7.75 (1 H, s); IR (KBr) 1678, 3256 cm^{-1}. Anal. Calcd for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 66.87; H, 6.89; N, 11.92.

4-Acetyl-1-benzyl-2-methylimidazole (16). 24 (180 mg, 0.77 mmol) was treated with sodium hydroxide (39 mg, 1.0 mmol) in ethanol (10 mL) at reflux for 2 h. Ammonium chloride (73 mg, 1.3 mmol) was added, and after this had substantially dissolved, the mixture was allowed to cool to room temperature and then concentrated in vacuo. The residue was flash chromatographed (ethyl acetate) to give 124 mg (75%) of pale yellow oil whose mass spectrum and ^1H NMR were identical with that of the product of benzylation of 4.

1-Benzyl-5-methylimidazole-4-carboxaldehyde (25). 11a (269 mg, 2.13 mmol) was hydrogenated at 45 psi over 10% palladium on carbon (135 mg) in ethanol (20 mL) at room temperature. After 1 h, the catalyst was removed by filtration and washed with ethanol. The filtrate was treated with benzylamine (2.28 g, 21.3 mmol); little reaction occurred during 24 h at room temperature, but after 4 h of reflux the hydrogenation product was consumed. Sodium hydroxide (94 mg, 2.34 mmol) was added, and reflux was continued for 1 h. Ammonium chloride (137 mg, 2.56 mmol) was then added, and after this had substantially dissolved, the mixture was allowed to cool to room temperature. The mixture was then concentrated in vacuo to a yellow oil, which was dissolved in 3 N hydrochloric acid (20 mL) and stirred at room temperature for 16 h. The mixture was then basified with solid sodium carbonate and extracted with chloroform (4 × 25 mL). The extract was dried over magnesium sulfate, filtered, and concentrated in vacuo. The residual oil was flash chromatographed (2.5:97.5 methanol/chloroform). The product obtained was contaminated with benzylamine, so it was rechromatographed, giving 82 mg (19%) of a yellow oil, which was an equal mixture of 1-benzyl-5-methylimidazole-4-carboxaldehyde (25) and 4-acetyl-1-benzylimidazole (26): mass spectrum, m/e (relative intensity) M^+, 200 (59.2), $M^+ - 15$, 185 (31.2, methyl ketone fragment), 91 (100); ^1H NMR ($CDCl_3$) δ 2.40 (3 H, s, ketone), 2.46 (3 H, s, aldehyde), 5.06 (2 H, s, aldehyde), 5.10 (2 H, s, ketone), 7.2 (10 H, m, aldehyde and ketone), 7.45 (1 H, s, ketone), 7.48 (1 H, s, aldehyde), 7.50 (1 H, s, ketone), 9.88 (1 H, s, aldehyde).

1-Benzyl-2,5-dimethylimidazole-4-carboxaldehyde (27). 11b (1.346 g, 9.60 mmol) was hydrogenated at 45 psi over 10% palladium on carbon (673 mg) in methanol (96 mL) at room temperature for 1 h. A second portion of catalyst (673 mg) was added, and the hydrogenation continued for another 1 h. The catalyst was removed by filtration and washed with methanol. The filtrate was treated with benzylamine (10.27 g, 96 mmol) and allowed to stir at room temperature overnight. Sodium hydroxide (422 mg, 10.6 mmol) was then added and the mixture refluxed for 3 h. Ammonium chloride (616 mg, 11.5 mmol) was added, and after this had substantially dissolved, the mixture was allowed to cool to room temperature. The solvent was removed in vacuo and the residue dissolved in ethyl acetate. This solution was washed with saturated ammonium chloride solution, dried with magnesium sulfate, filtered, and concentrated. The residual oil was flash chromatographed (5:95 methanol/chloroform), giving 370 mg (18%) of pale yellow oil: mass spectrum, m/e (relative intensity) M^+, 214 (36.9), 213 (12.0), 123 (14.7), 122 (15.2), 105 (19.8), 91 (100); ^1H NMR (CD_3OD) δ 2.30 (3 H, s), 2.43 (3 H, s), 5.15 (2 H, s), 7.2 (5 H, m), 9.88 (1 H, s); exact mass calcd for $C_{13}H_{14}N_2O$ 214.1106, found: 214.1104.

Acknowledgment. I thank G. Todd Miller for his technical assistance with the syntheses of **8b**, **9b**, and **27** and Carl J. Goddard who prepared **17** and **18**. In addition, I acknowledge the encouragement and guidance received from Professor E. J. Corey and Dr. J. L. LaMattina.

Reactions of 2-Cyclohexen-1-ones and Cyclohexane-1,3-diones with Chloro Methylene Iminium Salts

Alan R. Katritzky* and Charles M. Marson

Department of Chemistry, University of Florida, Gainesville, Florida 32611

Received October 6, 1986

Products are isolated and pathways established for the reactions of cyclohexane-1,3-diones with Vilsmeier reagents. Similarities between those reactions and the reactions of some 2-cyclohexen-1-ones with Vilsmeier reagents are demonstrated. The pathways proposed allow rationalization of products formed by the action of Vilsmeier reagents on a variety of cyclic and acyclic ketones.

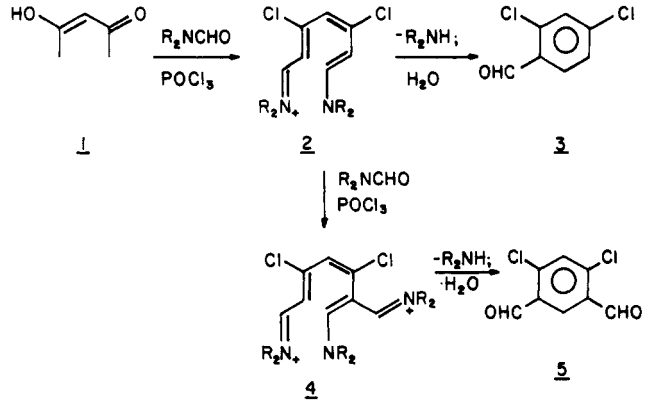
In 1965, Holy and Arnold reported[1] some synthetically useful iminoalkylations of unsaturated ketones. Only a brief indication of mechanism was given for these interesting reactions, among which was the formation of 2,4-dichlorobenzaldehyde (3) in high yield by the action of $DMF/POCl_3$ upon acetylacetone (1). In the present work, we sought a deeper understanding of the action of iminoalkylating reagents upon acyclic and cyclic diketones and, in particular, answers to the following: (i) what the pathways are by which diketones produce a variety of products; (ii) the nature of the products when an acyclic ketone was employed, instead of a cyclic ketone; and (iii) how an unsaturated monoketone would react compared to a diketone. The present study provides some of the answers.

In our hands, a mixture of $DMF/POCl_3$ acted on acetylacetone (1) to give exclusively 2,4-dichlorobenzaldehyde (3), as reported by Holy and Arnold[1] (Scheme I). However, the action of *N*-formylmorpholine/$POCl_3$ on acetylacetone (1) at 85 °C gave a separable mixture of 2,4-dichlorobenzaldehyde (3) (17%) and 4,6-dichloroiso-

(1) Holy, A.; Arnold, Z. *Collect. Czech. Chem. Commun.* **1965**, *30*, 47.

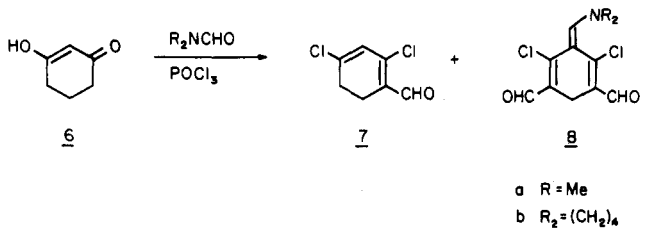
0022-3263/87/1952-2726$01.50/0 © 1987 American Chemical Society

Scheme I



phthalaldehyde (**5**) (29%); no other products were identified. We propose that the extensively delocalized iminium cation **2** eliminates R_2NH (presumably after electrocyclic ring closure) to give, after hydrolysis, 2,4-dichlorobenzaldehyde (**3**). Alternatively, when R_2N is relatively bulky (derived from morpholino rather than dimethylamino), cation **2** may undergo further iminoalkylation, producing dication **4**, which affords dialdehyde **5** by ring closure with elimination of R_2NH. Evidently, steric effects in an intermediate can markedly alter the products of an iminoalkylation reaction.

A paper by us[2] reported the formation of the novel, cross-conjugated dialdehyde *8a* by the action of DMF–

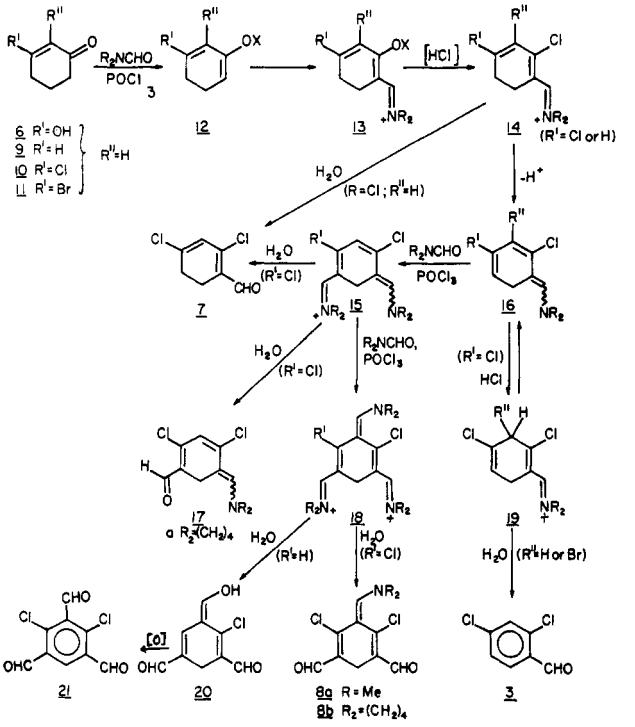


a R = Me
b $R_2 = (CH_2)_4$

$POCl_3$ upon cyclohexane-1,3-dione at 20 °C. That result is not an isolated example: successive replacement of DMF by *N*-methylformanilide, *N*-formylpyrrolidine, and *N*-formylmorpholine led to the isolation of three novel dialdehydes of type **8** (appropriate R).[3] Reaction of dialdehyde **8a** with either excess BF_3·Et_2O at 20 °C or excess 70% HNO_3 at 90 °C gave 1,3-dichloro-2,4,6-triformylbenzene in 17% and 30% yields, respectively (in the former case presumably by aerial oxidation). The stability of dialdehyde **8a** with respect to its benzenoid tautomer (and their noninterconversion) has been discussed elsewhere.[3].

It is remarkable that acetylacetone (**1**) and cyclohexane-1,3-dione (**6**) differing formally only by a methylene bridge, should give the dissimilar products **3** and **8**, respectively. However, the pathways postulated for the cyclic diketone in Scheme II resemble in most respects the mechanism for the acyclic analogue given in Scheme I. Thus, cation **15** (R′ = Cl) is formed from **6** (we believe, for reasons discussed later, via intermediates **12**, **13**, and **14**) in a manner similar to the formation of cation **2** from ketone **1**. However, whereas **2** can undergo ring closure, **15** could be hydrolyzed to give either the aldehyde **7** (**7** could also be formed by direct hydrolysis of **14**) or aldehyde **17**; alternatively, **15** is further iminoalkylated to give **18**, which is subsequently hydrolyzed to yield dialdehyde **8**.

Scheme II



The highly reactive aldehyde **7** was isolated in 24% yield by heating a mixture of $DMF/POCl_3$ and cyclohexane-1,3-dione (**6**) in $CHCl_3$ at 45 °C for 2 h. Use of *N*-formylpyrrolidine (in place of DMF) under the above reaction conditions gave aldehyde **17a** as a reaction intermediate detected by ^{13}C NMR and mass spectra. Treatment of this (neutralized) reaction mixture containing aldehyde **17a** with more *N*-formylpyrrolidine and $POCl_3$ gave crystalline dialdehyde **8b** (30% yield based upon ketone **6**), presumably via an intermediate of type **18**.

The reaction of 2-bromocyclohexane-1,3-dione with *N*-formylpyrrolidine/$POCl_3$ afforded 2,4-dichlorobenzaldehyde (**3**) in only 20% yield as the sole identified product. Instead of the further iminoalkylation necessary for the formation of intermediate **18** (and hence dialdehyde **8**), elimination of HBr takes place, presumably from cation **19** (R″ = Br), thereby affording aldehyde **3**. Interestingly, some of this pathway was also followed for the reaction[3] of cyclohexane-1,3-dione with *N*-formylpyrrolidine/$POCl_3$ at 20 °C to give dialdehyde **8b**; the mass spectrum of the oily product from the mother liquor showed intense signals at *m/z* 174 and 176, corresponding to the parent ion of the benzaldehyde **3**. It is likely that an *iminium cation*, such as **19** (R″ = H), undergoes oxidative aromatization followed by hydrolysis to give aldehyde **3**. Were an enamine such as **16** to aromatize directly (by double-bond migration), the product would contain a CH_2NR_2 moiety, as does the phenol **29** formed from cyclohexane-1,4-dione (**26**) vide infra).

The early steps in the pathway to dialdehyde **8a** were investigated by reacting 3-chloro-2-cyclohexen-1-one (**10**) and 3-bromo-2-cyclohexen-1-one (**11**) with $DMF/POCl_3$ at 20 °C; dialdehyde **8a** was isolated as the sole product of both reactions in yields of 43% and 59%, respectively, compared to only 24% when cyclohexane-1,3-dione (**6**) was used.[2] Although the intiial stages in reactions involving Vilsmeier reagents are not well understood,[4] the above results strongly suggest an intermediate of the form **12**

(2) Katritzky, A. R.; Marson, C. M. *Tetrahedron Lett.* **1985**, *26*, 4715.
(3) Katritzky, A. R.; Marson, C. M.; Palenik, G.; Koziol, A. E.; Luce, H.; Karelson, M.; Chen, B.-C.; Brey, W..; in preparation.

(4) Jutz, C. In *Iminium Salts in Organic Chemistry*; Boehme, H., Viehe, H. G., Eds.; Wiley: New York, 1976; Vol. 9, Part 1, pp 225–342.

which undergoes alkylation to give cation **13**. Presumably cation **13** undergoes attack by Cl^- at C–OX (and also at C–Br for R′ = Br), thereby affording cation **14**. Simple hydrolysis of **14** would form the aldehyde **7**, which, less plausibly, could also be formed by nucleophilic attack on cation **15**. The formation of the benzaldehyde **3** implicates both cation **14** and enamine **16**.

In 1979,[5] the action of DMF/$POCl_3$ on dimedone **22** was shown to give aldehydes **23** and **24**. In our hands, the reaction of *N*-formylmorpholine/$POCl_3$ with dimedone **22** at 20 °C afforded the dialdehyde **24** in 22% yield as an unstable oil, which rapidly dimerized with dehydration to give the yellow trialdehyde **25**, also reported by the previous workers.[5] Although in our experiments aldehyde **23** was not isolated, its formation and those of aldehydes **7** and **24**, from the respective cyclohexane-1,3-diones, support the intermediacy of enamines such as **15** and **16** (Scheme II). Pulst and co-workers[5] also showed that 3-chloro-5,5-dimethyl-2-cyclohexen-1-one was converted by DMF/$POCl_3$ into dialdehyde **24**, a fact consistent with our observation that 3-chloro-2-cyclohexen-1-one **10** afforded dialdehyde **8a** under similar conditions and with the general pathways of Scheme II). Additionally, those authors[5] showed that neither of the aldehydes **23** and **24** were formed by the action of DMF/$POCl_3$ on 1,3-dichloro-5,5-dimethylcyclohexa-1,3-diene. The action of DMF/$POCl_3$ upon 1,3-dichlorocyclohexa-1,3-diene was investigated by us, and again no dialdehyde **8a** was detected.

Although dialdehyde **24** is the expected product were the carbonyl groups in dimedone **22** to react independently, a more likely explanation is that a pathway analogous to **6** → **14** → **15** is followed. However, the *gem*-dimethyl analogue of dication **18** (R′ = Cl) could experience severe nonbonding interactions augmented by the *gem*-dimethyl groups. Even if such an analogue of **18** were formed, it might readily undergo C–C bond scission by nucleophilic attack to give the cation analogous to **15** and hence, by hydrolysis, dialdehyde **24**. Most probably, the reaction stops at the *gem*-dimethyl analogue of dication **15**, which then yields dialdehyde **24**.

The exothermic reaction of *N*-formylmorpholine/$POCl_3$ with 2-cyclohexen-1-one (**9**) in trichloroethylene at 20 °C afforded a deep red mixture, which was hydrolyzed to a bright yellow precipitate of the novel enol aldehyde **20**, obtained in 45% yield. A solution of enol aldehyde **20** in aqueous K_2CO_3 gave a ^{13}C NMR spectrum containing one aliphatic, five olefinic, and three aldehydic lines (24.4; 111.1–154.9; 181.5, 189.0, 194.0 ppm), as expected for the monoanion of aldehyde **20**. When compound **20** was kept at 25 °C for several weeks, trialdehyde **21** was formed, evidently by aerial oxidation; attempted sublimation of **20** also gave aldehyde **21** (50%).

The proposed pathway from 2-cyclohexen-1-one (**9**) to enol aldehyde **20** is also outlined in Scheme II (R′ = H); evidently the dialkylaminomethylene moiety of cation **18** (R′ = H) is more readily hydrolyzed than that of cation **18** (R′ = Cl). Notably, enol aldehyde **20** appears to be kinetically stable with respect to conversion into its benzenoid tautomer; however, **20** is oxidatively aromatized to trialdehyde **21** more readily than dialdehyde **8a** is hydrolytically oxidized to 1,3-dichloro-2,4,6-triformylbenzene. Related to the formation of trialdehyde **21** from enol aldehyde **20** is Rao and Raju's observation[6] that **21** is formed in 42% yield from 1,5-dimethoxy-1,4-cyclohexadiene.

Scheme III

Reaction of cyclohexane-1,4-dione (**26**) with *N*-formylmorpholine/$POCl_3$ at 20 °C in trichloroethylene afforded phenol **29** in 16% yield (Scheme III); no other major products were detected. That 4-chloro-3-(4-morpholinylmethyl)phenol (**29**) is the correct structure of the product is confirmed by the consistency of calculated and observed multiplicities and chemical shifts for the AMX system; the only other mechanistically plausible structure, namely, 4-chloro-2-(4-morpholinylmethyl)-phenol, does not fit the above ^1H NMR data; the mp of the latter[7] also differs markedly from that of phenol **29**.

The formation of phenol **29** could proceed via either or both of the intermediates **28** and **31**. Probably because those intermediates are not stabilized by a strongly electron-withdrawing group (as is cation **18**), aromatization of both intermediates **28** and **31** is expected to occur readily, giving phenol **29**. Interestingly, aerial oxidation of **28** and **31** to an aldehyde does not occur [contrast **19** (R″ = H) → **31**]. In contrast, the relative stability of cation **15** disfavors the formation of aldehyde **32**; instead further alkylation occurs, giving dication **18** and hence dialdehyde **8**.

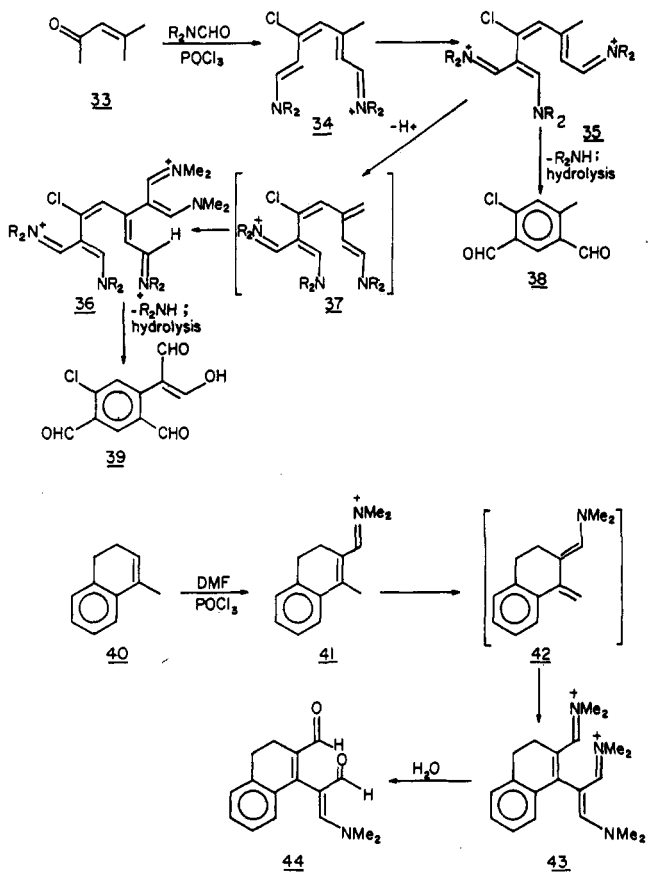
The formation of many other reported products of reactions involving Vilsmeier reagents can be rationalized in sequences analogous to those in Scheme II. Thus, mesityl oxide **33** affords[1] the surprising products **38** and **39** when treated with DMF/$POCl_3$ at 90 °C; the formation of stable polyiminium cations such as **35** and **36** and their subsequent electrocyclic ring closure determine the course of the reaction. In our hands, the reaction of 3,4-dihydro-1-methylnaphthalene (**40**) with DMF/$POCl_3$ at 80 °C afforded yellow prisms of the aldehyde **44**, even when only 2 mol of the Vilsmeier reagent was employed. That reaction illustrates the tendency to form polyiminium cations, so much so that the desired 2-formyl derivative of **40** was not detected. Styrenes, however, do undergo straightforward monoformylation to give cinnamaldehydes.[8]

Conclusions

The mechanistic pathways in Scheme II are consistent with all the observations and products herein reported, as well as with results reported by other workers.[1,5,6] Although chlorinated olefins are known to undergo iminoalkylation,[9]

(5) Pulst, M.; Hollborn, B.; Weissenfels, M. *J. Prakt. Chem.* **1979**, *321*, 671.

(6) Raju, B.; Krishna-Rao, G. S. *Synthesis* **1985**, 779.
(7) Julia, M.; Tchernoff, G. *Bull. Soc. Chim. Fr.* **1955**, 830.
(8) Schmidle, C. J.; Barnett, P. G. *J. Am. Chem. Soc.* **1956**, *78*, 3209.



intermediates such as 1,3-dichlorocyclohexa-1,3-diene do not appear to be involved in the reaction of cyclohexane-1,3-diones with Vilsmeier reagents.

Many of the products formed by reacting acyclic α,β-unsaturated ketones with Vilsmeier reagents can be rationalized by extending the mechanistic pathways proposed here (Scheme II). We are currently investigating the reactions of alkyl-substituted 2-cyclohexen-1-ones with Vilsmeier reagents.

Experimental Section

Melting points were determined on a Hoover Uni-melt capillary apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 297 spectrophotometer. ^{1}H NMR spectra were recorded with a Varian EM 360L spectrometer, and ^{13}C NMR spectra were recorded on a JEOL FX-100 spectrometer. "Evaporation" refers to removal of solvent under reduced pressure.

The following compounds were prepared by literature procedures: 2-bromocyclohexane-1,3-dione, mp 160.5–161.5 °C (lit.[10] mp 162–164 °C); 3-chloro-2-cyclohexen-1-one (**10**);[11] 3-bromo-2-cyclohexen-1-one (**11**);[11] 2,4-dichloro-1,5-diformyl-6,6-dimethylcyclohexa-1,4-diene (**24**);[5] 5,5′-(oxydimethylidyne)bis[2,4-dichloro-6,6-dimethyl-1,3-cyclohexadiene-1-carboxaldehyde] (**25**);[5] and 1,3-dichlorocyclohexa-1,3-diene.[11]

Reaction of Acetylacetone (1) with *N*-Formylmorpholine and Phosphorus Oxychloride. Phosphorus oxychloride (18.4 g, 0.12 mol) was added to *N*-formylmorpholine (14 g, 0.12 mol) so as to keep the temperature below 30 °C. The mixture was stirred 10 min, and acetylacetone (1.0 g, 10 mmol) was then added. That mixture was heated at 85 °C for 24 h, allowed to cool to 20 °C, and crushed ice added, so as to keep the temperature of the reaction mixture below 50 °C. The precipitate so obtained was filtered, washed with water, and dried to give 1.3 g of a 1:1 mixture of aldehydes **5** and **3**; trituration with cold ether (3 × 3 mL) afforded aldehyde **5** (0.60 g, 29%), which crystallized from 2-propanol as needles: mp 164–165 °C (lit.[12] mp 163 °C); ^{1}H NMR ($CDCl_3$) δ 10.30 (s, 2 H, CHO), 8.37 (s, 1 H, H-2), 7.54 (s, 1 H, H-5). Anal. Calcd for $C_8H_4Cl_2O_2$: C, 47.33; H, 1.99. Found: C, 47.34; H, 1.80.

The mother liquor of the filtrate (vide supra) was evaporated and the residue sublimed in vacuo to give aldehyde **3** (0.48 g, 27%, which crystallized from cyclohexane as needles: mp 68–70 °C (lit.[1] mp 69–71 °C); ^{1}H NMR ($CDCl_3$) δ 10.20 (s, 1 H, CHO), 7.67 (d, 1 H, J = 8 Hz, H-6), 7.33–7.13 (m, 2 H).

2,4-Dichloro-1-formylcyclohexa-1,3-diene (7). Phosphorus oxychloride (5.76 g, 26.6 mmol) was added over 2 min to a stirred solution of DMF (2.8 g, 38.3 mmol) in chloroform (15 mL) at 5 °C. The mixture was stirred for 10 min at 20 °C, cyclohexane-1,3-dione (1.68 g, 15 mmol) was then added, and the brown solution was heated at 45–50 °C for 2 h. The mixture was poured into a stirred mixture of chloroform (50 mL) and water (30 mL); after 10 min, the chloroform layer had become bright orange and was washed with water (3 × 30 mL), dried, and evaporated. The residual dark red oil (1.74 g) was triturated with 60–80 °C petroleum (4 × 15 mL), and the petroleum extracts were evaporated to give an oil, which on chromatography (30 g silica gel; 95:5 60–80 °C petroleum ether:ethyl acetate) afforded aldehyde **7** (0.65 g, 24 %) as a pale yellow oil that rapidly decomposed on standing but could be kept several hours at 0 °C in chloroform: IR (neat) 2955, 2855 (s), 2745, 1660 (vs), 1610, 1560 (s), 840, 815 (s), 785, 755 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 10.36 (s, 1 H, CHO), 6.28 (s, 1 H, vinyl), 2.70 (s, 4 H, CH_2CH_2); MS, m/z (rel intensity) 178 (M^+, ^{37}Cl, ^{35}Cl, 14), 176 (M^+, ^{35} Cl, ^{35}Cl, 23), 143 (15), 141 (50), 113 (43), 111 (52); HRMS, calcd 175.9796, found 175.9787.

Reaction of 2-Bromocyclohexane-1,3-dione with *N*-Formylpyrrolidine and Phosphorus Oxychloride. Phosphorus oxychloride (5.0 g, 32.6 mmol) was added over 2 min with stirring to *N*-formylpyrrolidine (4.0 g, 40 mmol) at 5 °C. 2-Bromocyclohexane-1,3-dione (1.91 g, 10 mmol) was added, keeping the temperature of the mixture below 10 °C. After stirring at 20 °C for 72 h, the mixture was poured into water (30 mL). Extraction with diethyl ether (2 × 20 mL), drying, and evaporation gave an oil (1.0 g) that when heated at 50 °C (1 mmHg) in a vacuum sublimation apparatus afforded aldehyde **3** (0.35 g, 20%), crystallizing from cyclohexane as needles: mp 67–69 °C (lit.[1] mp 69–71 °C) (^{1}H NMR data given above).

Reaction of 3-Chloro-2-cyclohexen-1-one with Dimethylformamide and Phosphorus Oxychloride. Phosphorus oxychloride (5.75 g, 37.5 mmol) was added over 2 min with stirring to DMF (10 mL) at 5 °C. Addition of 3-chloro-2-cyclohexen-1-one (0.196 g, 15 mmol) gave a solution that became hot after about 20 min. After stirring for 36 h at 20 °C, the mixture was poured into water (100 mL); sodium carbonate was added until the solution was neutral to pH paper. Extraction with dichloromethane (3 × 30 mL), drying, and evaporation gave an oil, which was triturated with diethyl ether. After 3 days at 0 °C, the precipitate was filtered to give dialdehyde **8a** (1.69 g, 43 %) as orange prisms, mp 146–150 °C; one recrystallization from chloroform gave an analytical sample, mp 149–150 °C, as previously reported.[2]

Reaction of 3-Bromo-2-cyclohexen-1-one with Dimethylformamide and Phosphorus Oxychloride. 3-Bromo-2-cyclohexen-1-one (2.63 g, 15 mmol) was used in place of 3-chloro-2-cyclohexen-1-one in the above procedure. Dialdehyde **8a** (2.71 g, 59 %), mp 146–150 °C, rising to 149–150 °C on recrystallization from chloroform, was the sole product.

Reaction of 2-Cyclohexen-1-one with *N*-Formylmorpholine and Phosphorus Oxychloride. To a solution of *N*-formylmorpholine (6.9 g, 60 mmol) in trichloroethylene (10 mL) was added phosphorus oxychloride (7.0 g, 46 mmol). The mixture was stirred for 10 min at 20 °C and 2-cyclohexen-1-one (1.5 g, 16 mmol) then added. An exothermic reaction occurred, the mixture becoming deep red. After stirring for 48 h, the clear liquid was decanted and water (40 mL) added to the residue. The mixture was vigorously stirred; after 10 min, the temperature had

(9) (a) Seitz, G. *Pharm. Zentralhalle* **1968**, *107*, 363; *Chem. Abstr.* **1968**, *69*, 76702. (b) Nazarov, I. N.; Zav'yalov, S. I. *Izv. Akad. Nauk. SSSR, Ser. Khim.* **1958**, 200. (b) Nazarov, I. N.; Zav'yalov, S. I. *Izv. Akad. Nauk. SSSR, Ser. Khim.* **1958**, 200.

(10) Nazarov, I. N.; Zaryalov, S. I. *Izvest. Akad. Nauk SSSR, Otdel. Khim. Nauk* **1958**, 200; *Chem. Abstr.* **1958**, *52*, 12775c.

(11) Crossley A.; Haas, P. *J. Chem. Soc.* **1903**, *83*, 494.

(12) *Chem. Zentralbl.* **1912**, *1*, 763; *Dictionary of Organic Compounds*, 5th ed.; Buckingham, J., Donaghy, S. M., Eds.; Chapman and Hall: New York, 1982.

risen to above 60 °C with the formation of a bright yellow precipitate. Filtration and washing with water gave crude enol aldehyde **20** (1.4 g, 45%): mp 97–102 °C; IR ($CHBr_3$) 1625, 1580, 1225, 1205, 985 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 10.50 (d, 1 H, J = 2 Hz), 10.18 (m, 1 H), 8.67–7.40 (m, 3 H), 3.33 (s, 2 H); ^{13}C NMR (MeOH) 194.0 (d), 189.0 (d), 181.5 (d), 154.9 (s), 146.6 (d), 125.1 (s), 117.3 (s), 111.1 (s), 24.4 (t) ppm. Anal. Calcd for $C_9H_7ClO_3$: C, 54.43; H, 3.55. Found: C, 54.33; H, 3.40.

Attempts to purify enol aldehyde **20** led to decomposition; vacuum sublimation afforded trialdehyde **21** in 39% yield as reported elsewhere.[13] However, solutions of **20** in aqueous potassium carbonate were stable at 20 °C for several weeks.

4-Chloro-3-(4-morpholinylmethyl)phenol (29). To a solution of *N*-formylmorpholine (13.7 g, 0.119 mol) in trichloroethylene (20 mL) was added phosphorus oxychloride (14 g, 91.3 mmol). The mixture was stirred for 10 min at 20 °C, placed in an ice–water bath, and cyclohexane-1,4-dione (3.36 g, 30 mmol) then added; the temperature of the very exothermic reaction was kept below 50 °C. After 72 h, the mixture was poured into dichloromethane (50 mL) and water (50 mL); solid sodium carbonate was added with constant stirring until the aqueous layer was neutral. The organic layer was dried and evaporated to give an oil, which on trituration with 1:9 chloroform:trichloroethylene afforded phenol **29** (1.26 g, 16%) that crystallized from isopropyl alcohol as prisms: mp 133–134 °C; IR ($CHBr_3$) 3400 (bd), 1560, 1465, 1440, 905, 870, 855, 810 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 9.73 (s, 1 H, OH), 7.30 (d, 1 H, J = 9 Hz), 7.05 (d, 1 H, J = 3 Hz), 6.80 (dd, 1 H, J = 3 and 9 Hz), 3.80–3.30 (m, 6 H), 2.60–2.30 (m, 4 H). Anal. Calcd for $C_{11}H_{14}ClNO_2$: C, 58.02; H, 6.20; N, 6.15. Found: C, 58.01; H, 6.31; N, 5.93.

1-(2-(*N*,*N*-Dimethylamino)-1-formylvinylene)-3,4-dihydronaphthalene-2-carboxaldehyde (44). Phosphorus oxychloride (10.5 g, 68.5 mmol) was added over 2 min with stirring to DMF (10 g, 0.137 mmol) at 5 °C. Addition of 3,4-dihydro-1-methylnaphthalene[14] (3.0 g, 20.8 mmol) gave a mixture that was heated at 80 °C for 14 h. The dark solution was poured into 10% aqueous sodium acetate (150 mL) and the mixture extracted with dichloromethane (2 × 50 mL). The organic layers were combined, washed first with 5% aqueous sodium acetate and then with water, dried, and evaporated to afford a residue that was triturated with 60–80 °C petroleum (2 × 30 mL). The gum remaining was dissolved in chloroform (1 mL) and eluted through silica gel (30 g) by using consecutively as eluents ethyl acetate, chloroform, and dichloromethane. All the eluents were combined and evaporated to give an oil (1.4 g), which on trituration with 60–80 °C petroleum (10 mL) gave aldehyde **44** (0.94 g, 18%) that crystallized from ethyl acetate as yellow needles: mp 133–134 °C; IR ($CHBr_3$) 2950, 2890, 2840, 1640, 1600 (vs, broad), 1560, 905, 855, 750 cm^{-1}); ^1H NMR ($CDCl_3$) δ 9.70 (s, 1 H), 9.10 (s, 2 H), 7.20 (s, 4 H), 2.80 (s, 7 H). Anal. Calcd for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49. Found: C, 75.30; H, 6.80;, N, 5.46.

Acknowledgment. This work was supported in part by the donors of the Petroleum Research Fund, administered by the American Chemical Society. We thank the Instrument Program, Chemistry Division, National Science Foundation, for a grant for the Nicolet NT-300 spectrometer (at the University of Florida) and Professor G. S. Krishna-Rao for his comments on the draft of this and the following paper and for informing us of his own work.

Registry No. **1**, 123-54-6; **3**, 874-42-0; **5**, 108009-48-9; **7**, 108009-49-0; **8a**, 101392-95-4; **9**, 930-68-7; **10**, 5682-75-7; **11**, 56671-81-9; **20**, 108009-50-3; **26**, 637-88-7; **29**, 108009-51-4; **40**, 4373-13-1; **44**, 108009-52-5; DMF, 68-12-2; $POCl_3$, 10025-87-3; *N*-formylmorpholine, 4394-85-8; cyclohexane-1,3-dione, 504-02-9; *N*-formylpyrrolidine, 3760-54-1; 2-bromocyclohexane-1,3-dione, 60060-44-8.

(13) Katritzky, A. R.; Marson, C. M.; Wang, Z., in press.

(14) Garbisch, E. W. *J. Org. Chem.* **1961**, *26*, 4165.

Reactions of Alkyl-Substituted 2-Cyclohexen-1-ones with Vilsmeier Reagents

Alan R. Katritzky,* Charles M. Marson, and Zuoquan Wang

Department of Chemistry, University of Florida, Gainesville, Florida 32611

Received October 6, 1986

Various 2-cyclohexen-1-ones underwent formylation on treatment with formamides and $POCl_3$ at 20 °C. Two distinct reactivity patterns were found: type A, in which mono-, di-, or triformylated olefins or benzenes are formed, and type B, in which a 3-methyl-2-cyclohexen-1-one undergoes formylation at the carbon atom of the 3-substituent. Several 2-cyclohexen-1-ones afford formylated products analogous to those obtained from the reaction of 3-oxo-4-ene steroids with Vilsmeier reagents. Mechanistic rationales for several Vilsmeier reactions are proposed.

Whereas β-chlorovinyl aldehydes are the normal products from the reaction of cyclohexanones with Vilsmeier reagents,[1] cyclohexane-1,3-diones can give rise to a variety of formylated products.[2,3] Cyclohexane-1,3-diones exist predominantly in solution at 20 °C in a monoenol form which contains both olefinic and ketonic moieties. Alicyclic olefins can themselves form more than one product under Vilsmeier conditions (e.g.,[4] **2** → **1** and **3**), whereas 3-oxo-4-ene steroids **5** can give monoformylated structures (e.g., **4**,[5] **8b**,[6] and **8c**[6]), diformyl benzenoid derivatives (e.g., **6**[5]), or simply chloroolefins (e.g., **8a**[6]). We classify these reaction pathways as types A1, A2, and B (Scheme I).

We now report a systematic study of the reaction of alkyl-substituted 2-cyclohexen-1-ones with Vilsmeier reagents. Our aims were to extend the scope of such formylation reactions and to provide some rationale for the products of those reactions, whether reported here or previously.

Reaction of 4-isopropyl-2-cyclohexen-1-one with a 1.3:1 molar ratio of *N*-formylmorpholine/$POCl_3$ in trichloro-

(1) Pulst, M.; Weissenfels, M. *Z. Chem.* **1976**, *16*, 337.
(2) Katritzky, A. R.; Marson, C. M. *Tetrahedron Lett.* **1985**, *26*, 4715.
(3) Pulst, M.; Hollborn, B.; Weissenfels, M. *J. Prakt. Chem.* **1979**, *321*, 671.
(4) Grimwade, M. J.; Lester, M. G. *Tetrahedron* **1969**, *25*, 4535.
(5) Laurent, H.; Wiechert, R. *Chem. Ber.* **1968**, *101*, 2393.
(6) Sciaky, R.; Mancini, F. *Tetrahedron Lett.* **1965**, *2*, 137.

0022-3263/87/1952-2730$01.50/0 © 1987 American Chemical Society