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OXIDATIVE FORMYLATION AND CHLOROMETHYLATION IN VILSMEIER REACTIONS OF *O*- AND *S*-HETEROCYCLIC KETONES

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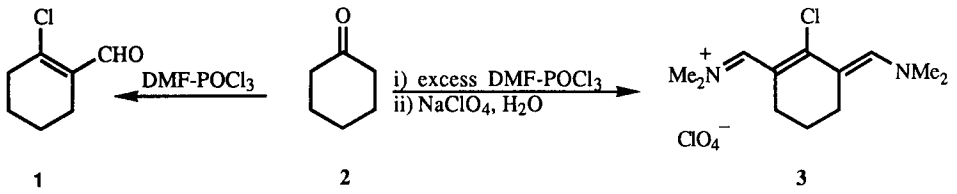
Abstract: The action of DMF-$POCl_3$ at 20 °C on tetrahydro-4*H*-pyran-4-one, tetrahydro-4*H*-thiopyran-4-one, chroman-4-one, and thiochroman-4-one affords the corresponding β-chlorovinylaldehydes. However, with excess DMF-$POCl_3$ at 100 °C, chroman-4-one affords 3-(chloromethyl)chromone, and thiochromanone gives 3-formylthiochromone. Mechanistic rationalisations are provided.

INTRODUCTION

The Vilsmeier-Haack-Arnold reaction,[1] a valuable means of introducing a formyl group into an activated aromatic ring, depends on the ability of the chloromethyleniminium species involved to undergo attack by *C*-nucleophiles. The action of Vilsmeier reagents on ketones is less well understood, but also involves attack of iminium species by *C*-nucleophiles; the products usually contain β-chlorovinylaldehyde moieties.[2] The products from those reactions are known to be influenced particularly by the cyclic[2,3] or acyclic[1a,2] nature of the ketone, the presence of double bonds,[3] and by certain oxygen-containing functional groups.[3]

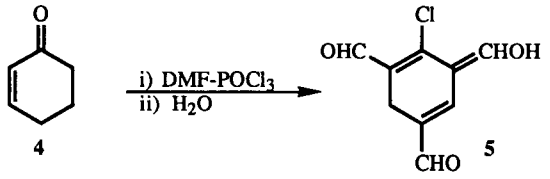
The reaction of carbocyclic ketones with Vilsmeier reagents is well-documented.[2,3,4] With 1-2 equivalents of the Vilsmeier reagent, cyclohexanone (**2**) affords the β-chlorovinylaldehyde **1** in good yield;[5,6] however, the reaction of excess Vilsmeier reagent, followed by addition of sodium perchlorate solution afforded the 3-chloropentamethinium salt **3**.[7]



1 **2** **3**

Scheme 1

The behaviour of 2-cyclohexen-1-one (**4**) with DMF-$POCl_3$ is more complex still, the enol dialdehyde **5** being formed.[3a]



Scheme 2

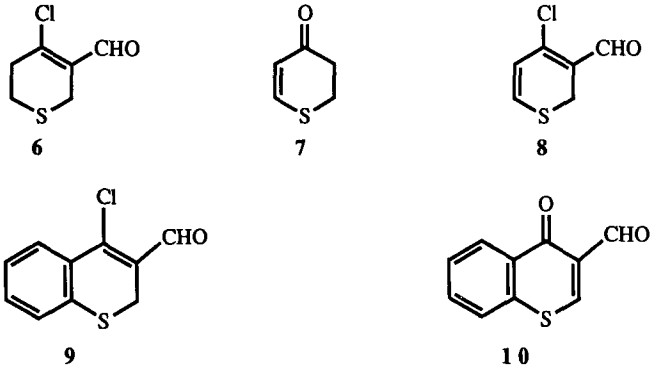
The action of Vilsmeier reagents on a variety of substituted 2-cyclohexen-1-ones has been studied;[3b,8] although there is usually one major product, several different types of aldehyde can be formed. Pathways to the products have been elucidated, although prediction of the actual products is not usually possible at this time. Accordingly, since the effect of incorporating a single heteroatom into a monocyclic system containing a carbonyl group capable of reaction with a Vilsmeier reagent is virtually unexamined,[9] we investigated the reactions of some monocyclic six-membered *O*- and *S*-heterocycles with DMF-$POCl_3$. Also reported here are new observations concerning the effect of temperature on the reaction of DMF-$POCl_3$ with polycyclic ketones (*e.g.* chroman-4-one[10a]) containing one heteroatom and a carbonyl group in a ring fused to one or more aromatic rings.[10]

RESULTS AND DISCUSSION

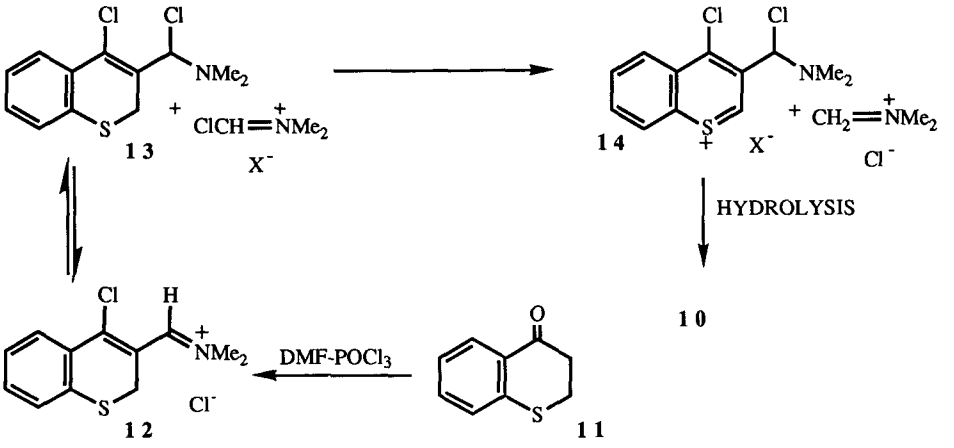
(a) *S*-Heterocycles

Tetrahydro-4*H*-thiopyran-4-one[11] was converted by DMF-$POCl_3$ at 20 °C into a mixture which after hydrolysis with aqueous sodium acetate afforded 4-chloro-5,6-dihydro-2*H*-thiopyran-3-carboxaldehyde (**6**) in 52 % yield. In view of the complex and anomalous reactions of several 2-cyclohexen-1-ones, as compared with cycloalkanones, with Vilsmeier reagents, the behaviour of 2,3-dihydro-4*H*-thiopyran-4-one (**7**)[12] towards DMF-$POCl_3$ at 20 °C was studied; 4-chloro-2*H*-thiopyran-3-carboxaldehyde (**8**) was isolated in 30% yield. It is interesting that no formylation at C-5 was observed, and in this respect, the endocyclic double bond behaves as do α,α-dialkyl substituents to a carbonyl group, preventing formylation at the α-carbon atom, and directing formylation to the α'-site.

The effect of benzannelation on the course of the reaction was then examined: the action of DMF-$POCl_3$ on thiochroman-4-one at 20 °C afforded β-chlorovinylaldehyde **9** using essentially the reaction conditions described by Weissenfels and co-workers.[10b] However, under more forcing conditions, (5 eq. DMF-$POCl_3$, 100°C, 4 days) we isolated 3-formylthiochromone (**10**),[13] in 29%, yield, together with aldehyde **9** in 40% yield.



The formation of enone **10** constitutes an oxidation in the presence of a Vilsmeier reagent. It is likely that the salt **12** would be in equilibrium with the neutral heterocycle **13** which could undergo oxidation by the chloromethyleniminium species (not necessarily direct hydride-transfer) to the substantially aromatic benzo[*b*]thiopyrylium system **14**, presumably with concomitant formation of the methyleniminium species. In this mechanism the Vilsmeier reagent is postulated as the oxidant.

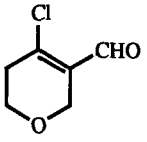


Scheme 3

(b) *O*-Heterocycles

Room temperature was selected in view of the known cleavage of tetrahydropyrans by Vilsmeier reagents at higher temperatures.[14] The action of DMF-$POCl_3$ on tetrahydropyran-4-one in trichloroethylene at 20 °C afforded the aldehyde **15** in 44 % yield. The reaction of chroman-4-one with DMF-$POCl_3$ at 25 °C for 3 h gave no discernible products. It had been noted that the aldehyde **16** had been formed in 36% yield under the conditions reported by

Weissenfels and co-workers,[10b] namely at 35 °C for 3 h using trichloroethylene as the solvent; we formed aldehyde **16** at 65 °C.



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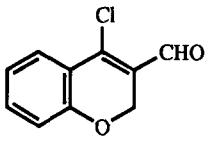

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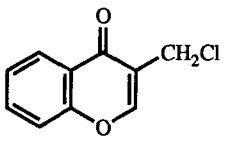
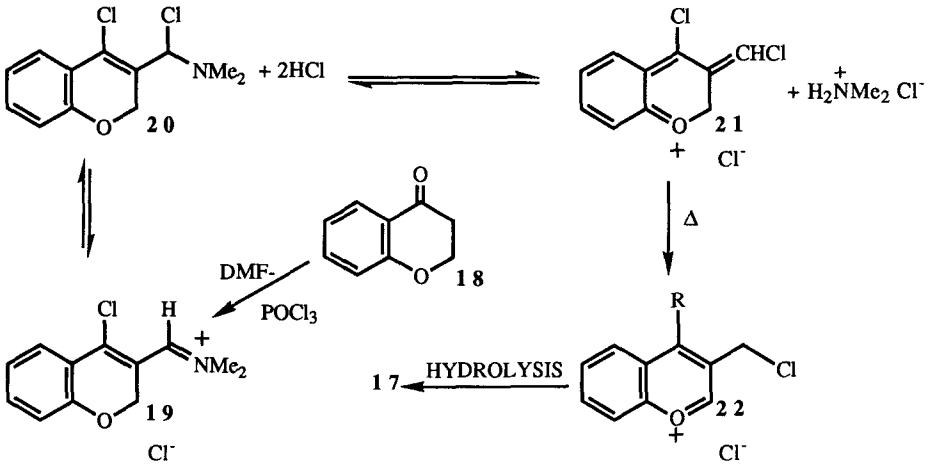


17

Treatment of chroman-4-one with 5 equiv. $POCl_3$ in DMF as solvent at 100 °C for 3 days afforded 3-(chloromethyl)chromone (**17**) in 48% yield. Generation of a chloromethyl group from a chloromethyleniminium species is apparently without precedent. Notably, treatment of *o*-hydroxyacetophenone with excess DMF-$POCl_3$ afforded 3-formylchromone.[15] A benzo[*b*]pyrylium system, well-known for its thermodynamic stability[16] may be involved (scheme 4). Expulsion of the aminoalkyl group would afford a stabilised oxonium cation **21** whose conversion (either directly [R=Cl] or indirectly [R=Cl or differently substituted **20** or **21**) to an aromatic benzo[*b*]pyrylium ring **22** is evidently favoured at temperatures around 100 °C.



Scheme 4

The reaction of substituted chroman-4-ones with Vilsmeier reagents has been extensively investigated by other groups,[10a,17] and illustrates well the interplay of steric and electronic effects in Vilsmeier-Haack reactions with various heterocyclic ketones; thus, 2,2-dimethylchroman-4-one is converted mainly into the 4-chloro-2*H*-chromene, the small quantity of β-chlorovinylaldehyde not being increased with prolonged reaction times; instead, formylation at position-6 occurs. Benzo[*f*]chromanone[10c,18] and benzo[*h*]-chromanone[18] have also been converted into the corresponding β-chlorovinylaldehydes.

The present study shows that simple monocyclic β-chlorovinylaldehydes containing either an oxygen or sulphur atom can be prepared; further formylation was not observed. Similarly, 2,3-dihydro-4*H*-thiopyran-4-one (**7**) is converted into 4-chloro-2*H*-thiopyran-3-carboxaldehyde (**8**), the lack of formylation at the 5-position being notable. Additionally, in the reactions of chroman-4-one and thiochromanone with DMF-$POCl_3$, elevated temperatures have been shown to give products constitutionally different from the usual *β*-chlorovinylaldehydes, but formylation of the benzene ring was not observed under any of the conditions we employed.

EXPERIMENTAL

General Details. - All melting points were determined with a Kofler hot-stage apparatus and are uncorrected. NMR spectra were run in $CDCl_3$; chemical shifts are quoted in ppm downfield from internal tetramethylsilane; line separations (*J*) are expressed in Hertz. ^1H NMR spectra were determined on a Perkin Elmer R-34 spectrometer operating at 220 MHz, and ^{13}C (and some ^1H) NMR spectra on a Bruker AM-250 instrument operating at 62.9 and 250 MHz respectively. The following abbreviations are used to describe NMR signals: s, singlet; d, doublet; dd double doublet; t, triplet; q, quartet; m, multiplet; b, broad. Mass spectra were obtained on a Kratos MS-25 instrument, operating in chemical ionisation (CI) or electron impact (EI) mode, as specified. Infra-red spectra were obtained on Perkin-Elmer 684 or 157G instruments as a thin film or in chloroform solution. Microanalytical data were obtained on a Perkin-Elmer 2400 CHN instrument. Yields are for material assessed as homogeneous by thin-layer chromatography and ^1H NMR spectroscopy. Thin-layer chromatography was performed on Merck 0.2 mm aluminium-backed silica plates and visualised using ultra-violet light, or developed using ceric sulphate spray. Column chromatography was performed using Merck silica gel 60 (230-400 mesh) under gravity. Petroleum ether (40-60 fraction) and ethyl acetate were distilled prior to use. Evaporation refers to the removal of solvent under reduced pressure, unless otherwise stated. Ketonic starting materials were purchased from Aldrich, with the exception of thiopyranone **7**.

4-*Chloro*-5,6-*dihydro*-2H-*thiopyran*-3-*carboxaldehyde* (**6**).-Phosphorus oxychloride (1.5 g, 9.8 mmol) was added to an ice-cold, well-stirred solution of DMF (0.65 g, 9.8 mmol) in trichloroethylene (10 ml). The mixture was stirred at 5 °C for a further 5 min, then allowed to warm to room temperature over 10 min; tetrahydrothiopyran-4-one (0.25 g, 0.21 mmol) was added, and the mixture stirred at 20 °C for 16 h. Aqueous sodium acetate solution (50 ml; 20%) was added, the organic layer separated, and the aqueous layer extracted with dichloromethane (3 x 50 ml). The combined organic layers were washed with sodium hydrogen carbonate solution, dried (magnesium sulphate), and the solvent evaporated to give a brown oil which was purified by column chromatography using ethyl acetate-petroleum ether (1:9) as eluant to give the *aldehyde* **6** (160 mg, 52%) as a colourless oil (Found: C, 44.47; H, 4.15; Cl, 21.41. C_6H_7ClOS requires C, 44.44; H, 4.31; Cl, 21.60 %);

$\nu_{max.}$(film) 1675, 1620, and 905 cm^{-1}; δ_H 10.2 (1H, s, CHO), 3.36 (2H, s, H-2), and 2.84 (4H, m, H-5 and H-6); δ_C 189.4 (d), 152.1 (s), 132.3 (s), 37.0 (t), 25.7 (t), and 24.9 (t); *m/z* (EI) 162 (M^+, 100%), 151(22), 133(22), 127(50), and 99 (61); 2,4-DNP derivative, reddish-brown prisms, m.p. 258-260 °C (from acetic acid-water) (Found: C, 41.93; H, 3.11; N, 15.81; Cl, 10.27. $C_{12}H_{11}ClN_4O_4S$ requires C, 42.05; H, 3.23; N, 16.35; Cl, 10.34%).

2,3-*Dihydrothiopyran*-4-*one* (**7**).-2,3-Dihydrothiopyran-4-one was prepared by a modification of the method as described by Chen, Reynolds, and Van Allan.[12] In our hands, precipitation of the succinimide with diethyl ether was incomplete; however, column chromatography was found to elute a small quantity of tetrahydrothiopyran-4-one, followed by a pure sample of 2,3-dihydrothiopyran-4-one. *N*-Chlorosuccinimide (0.6 g, 0.43 mmol) was added over 10 min to a well-stirred solution of tetrahydrothiopyran-4-one (0.5 g, 0.43 mmol) and pyridine (0.34 g) in dichloromethane (50 ml) maintained at 5 °C, and stirring was continued for a further 2 h, then at 20 °C for 12 h. The bulk of the solvent was evaporated, and the remaining viscous oil was purified by column chromatography using dichloromethane as eluant to give the *ketone* **7** (0.35 g, 71%) as a colourless oil; δ_H 7.5 (1H, d, H-2), 6.15 (1H, d, H-3), 3.25 (2H, t, H-6), and 2.71 (2H, t, H-5), *m/z* (EI) 114 (M^+, 40%), 86 (100), 58 (51), and 45 (12).

4-*Chloro*-2H-*thiopyran*-3-*carboxaldehyde* (**8**).- Phosphorus oxychloride (1.2 g, 7.8 mmol) was added to an ice-cold, well-stirred solution of DMF (0.58 g, 7.8 mmol) in trichloroethylene (10 ml). The mixture was stirred for an additional 5 min, then allowed to warm to room temperature over 10 min; 2,3-dihydrothiopyran-4-one (0.3 g, 0.26 mmol) was added and the mixture stirred at 20 °C for 15 h. Aqueous sodium acetate solution (50 ml) was added, the organic layer separated, and the aqueous layer extracted with dichloromethane (3 x 50 ml). The combined organic layers were washed with sodium hydrogen carbonate solution, dried (magnesium sulphate), and the solvent evaporated to give a brown oil, which was purified by column chromatography using ethyl acetate-petroleum ether (1:9) as eluant, to give the *aldehyde* **8** (110 mg, 30%) as a bright yellow oil which rapidly decomposed (Found: C, 45.37; H; 3.48. C_6H_5OSCl requires C, 44.86; H, 3.11%); $\nu_{max.}$ 2870, 1665, 1585, 1510, and 985 cm^{-1}; δ_H 10.1 (1H, s, CHO), 6.98 (1H, d, J =10 Hz), 6.33 (1H, d, J =10 Hz), and 3.70 (2H, t, H-2); δ_C 184.4 (d), 145.1 (s), 138.1 (d), 124.7 (d), 115.9 (s), and 23.2 (t); *m/z* (EI) 160 (M^+, 55%), 131 (100), 97 (54), and 45 (53); 2,4-DNP derivative, orange-red prisms, m.p. 216-218 °C (from acetic acid-water) (Found: C, 41.96; H, 2.60; N, 16.31; S, 9.75; Cl, 10.26. $C_{12}H_9ClN_4O_4S$ requires C, 42.30; H, 2.66; N, 16.45; S , 9.41; Cl, 10.41 %).

3-*Formylthiochromone* (**10**).-Phosphorus oxychloride (2.5 g, 16.2 mmol) was added slowly to ice-cold, stirred DMF (1.2 g) over 5 min. The mixture was allowed to warm to room temperature over 10 min; thiochroman-4-one (0.5 g, 3.2 mmol) was then added, and the mixture heated at 100 °C for 4 days. Aqueous sodium acetate solution (50 ml) was added, the organic layer separated, and the aqueous layer extracted with dichloromethane (3 x 50 ml). The combined organic layers were washed with sodium hydrogen carbonate solution,

dried (magnesium sulphate), and the solvent evaporated to give a brown oil which was purified by column chromatography using ethyl acetate-petroleum ether (1:4) as eluant to elute first 4-*chlorothiochroman*-3-*carboxaldehyde* (**9**) (300 mg, 40%) obtained as a bright yellow oil and then 3-*formylthiochromone* (**10**) (170 mg, 29%) obtained as brown prisms, m.p. 162-163 °C (from ^{i}PrOH) lit.,[19] 165 °C (Found: C, 62.67; H, 3.13; S, 17.06. $C_{10}H_6O_2S$ requires C, 63.14; H, 3.17; S, 16.85%); $\nu_{max.}$ 1680, 1625, and 1210 cm^{-1}; δ_H (250 MHz) 10.42 (1H, s, CHO), 8.81 (1H, s, H-2), 8.68 (1H, m, H-5), and 7.7 (3H, m, H-6, H-7 and H-8); δ_C 187.3 (d), 178.6 (s), 146.0 (d), 135.6 (s), 133.3 (s), 132.4 (d), 129.1 (s), 129.0 (d), 128.9 (d), and 127.2(d); *m/z* (CI) 191 (M+1, 100 %), 162 (72), and 134 (12).

4-*Chloro*-5,6-*dihydro*-2*H*-*pyran*-3-*carboxaldehyde* (**15**).-Phosphorus oxychloride (1.14 g, 0.74 mmol) was added to an ice-cold, well-stirred solution of DMF (0.54 g, 0.74 mmol) in trichloroethylene (10 ml). The mixture was allowed to stir at 5 °C for a further 5 min, then allowed to warm to room temperature. Tetrahydropyran-4-one (0.5 g, 0.5 mmol) was then added and the mixture was stirred at 20 °C for 16 h. Aqueous sodium acetate solution (50 ml; 20%) was added, the organic layer separated, and the aqueous layer extracted with dichloromethane (3 x 50 ml). The combined organic layers were washed with sodium hydrogen carbonate solution, dried (magnesium sulphate), and the solvent evaporated to give a brown oil which was purified by column chromatography using ethyl acetate-petroleum (1:9) as eluant to yield the *aldehyde* **15** (320 mg, 44 %) as a colourless oil which rapidly decomposed (Found: C, 48.43; H, 4.57. $C_6H_7ClO_2$ requires C, 49.17; H, 4.81%); $\nu_{max.}$ 2970, 1730, 1675, 1645, 1250, and 900 cm^{-1}; δ_H 10.07 (1H, s, CHO), 4.31 (2H, s), 3.82 (2H, t, *J* =5 Hz), and 2.65 (2H, m); δ_C 188.4 (d), 147.2 (s), 132.5 (s), 64.4 (t), 64.0 (t), and 34.6 (t); *m/z* (EI) 146 (M^+, 62%), 117 (78), and 53 (100); 2,4-DNP derivative, reddish-brown prisms, m.p. 198-200 °C (from acetic acid-water) (Found: C, 44.05; H, 3.32; N, 17.08. $C_{12}H_{11}ClN_4O_5$ requires C, 44.12; H, 3.39; N, 17.15%).

3-*(Chloromethyl)chromone* (**17**).-Phosphorus oxychloride (2.2 g, 14.3 mmol) was added slowly to DMF (3 g) at 5 °C over 5 min. The mixture was allowed to warm to room temperature over 10 min; chroman-4-one (0.5 g, 3.3 mmol) was added and the mixture heated at 100 °C for 3 days. Aqueous sodium acetate solution (50 ml) was added, the organic layer separated, and the aqueous layers extracted with dichloromethane (3 x 50 ml). The combined organic layers were washed with sodium hydrogen carbonate solution, dried (magnesium sulphate), and the solvent evaporated to yield a brown oil which was purified by column chromatography using ethyl acetate-petroleum ether (1:9) as eluant to give 3-*(chloromethyl)chromone* **17** (311 mg, 48%) as pale yellow plates, m.p. 109-110 °C (lit.,[20] m.p. 108.5-109 °C, $\nu_{max.}$ 3020, 1650, 1465, and 1210 cm^{-1} ; δ_H 8.20 (1H, dd, *J* =6 and 0.5 Hz), 8.08 (1H, s), 7.65 (1H, t, *J* =6 Hz), 7.5-7.3 (2H, m), and 4.51 (2H, s); δ_C 175.9 (s), 156.4 (s), 154.6 (d), 133.9 (d), 125.9 (d), 125.5 (d), 123.7 (s), 121.5 (s), 118.1 (d), and 37.5 (t); *m/z* 194.0135. $C_{10}H_7O_2{}^{35}Cl$ requires 194.0136.

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