SYNTHESIS AND PROPERTIES OF 3-FORMYL-4H-PYRANS

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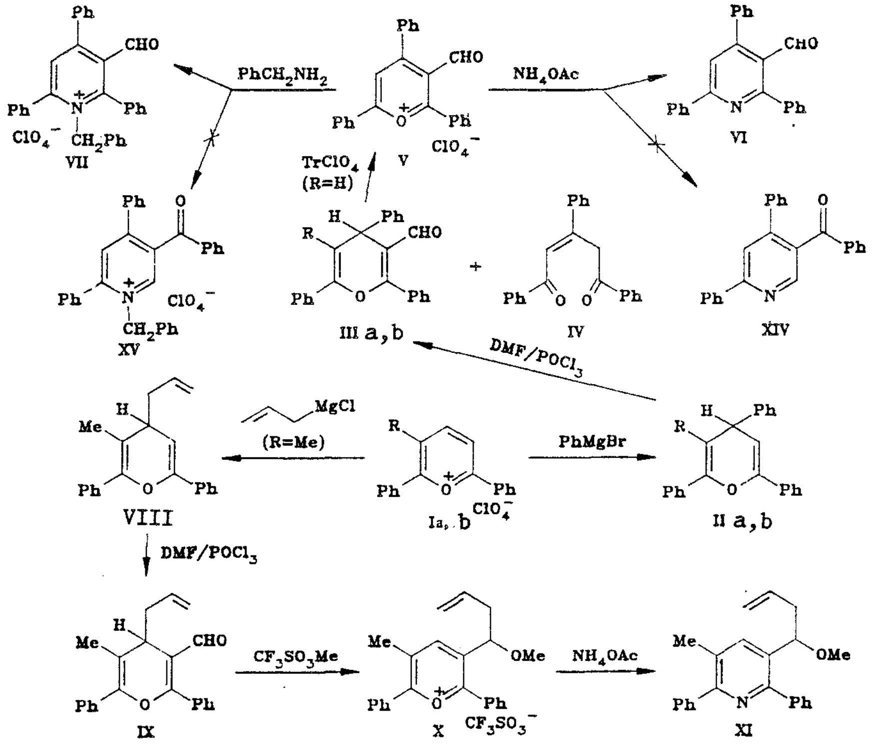
The Vilsmeier formylation of 4H-pyrans afforded 3-formyl-4H-pyrans. These were converted to 3-formylpyrylium salts, from which pyridine or pyridine salts with an aldehyde group at $C_{(3)}$ *were obtained. The reaction between 3-formyl-4-allyl-4H-pyran and methyltrifluoromethanesulfonate proceeded via a Koop rearrangement.*

An important reaction widely used in organic synthesis is the oxidation of the 4H-pyrans to pyrylium salts [1, 2]. A problem encountered in attempts to expand the synthetic possibilities of the pyrylium cation has been the difficulty in introducing functional groups into the pyran and pyrylium ring.

In the present work, we studied the possibility of carrying out the electrophilic substitution of pyrans. In particular, we concentrated on the introduction of an aldehyde group into the ring, and we prepared and studied some formyl derivatives.

The starting compounds for the formylation – 4H-pyrans IIa and b and VIII – were obtained by the reaction of a 4-unsubstituted pyrylium salt (Ia, b) with a Grignard reagent.



I—III a R=H; b R=Me

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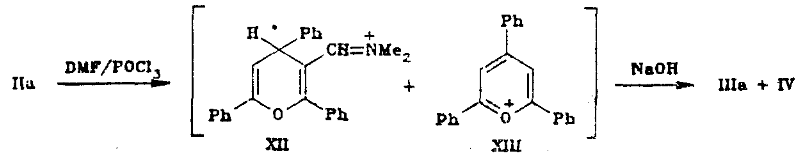
We found that the main process in the reaction of compounds IIa, IIb, and VIII with the Vilsmeier reagent was electrophilic attack at position 3 of the pyran ring. A side reaction was the oxidative dehydration of the starting pyrans to give pyrylium salts; this was demonstrated by the isolation of the diketone IV, in addition to the aldehyde IIIa, after treatment of the reaction mixture with alkali. This is consistent with the hydrolysis of the intermediate compounds XII and XIII:

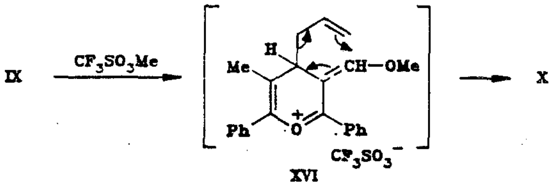


It is interesting to note that in the formylation of the 4H-chromenes, reported earlier [3, 4], oxidation to 1-benzopyrylium cations was not detected. In the case of 2,4-diphenyl-4H-chromene, the 3-formyl derivative was formed almost quantitatively [4]. This suggests that the pyrans are more readily oxidized to pyrylium salts than the chromenes; possibly because the pyrylium cation has more aromatic character than the 1-benzopyrylium cation.

When treated with tritylperchlorate, 3-formylpyran IIIa formed the 3-formylpyrylium salt V in high yield. In an analogous reaction with 2-phenyl-3-formyl-4H-chromene, no 2-phenyl-3-formyl-1-benzopyrylium perchlorate was isolated [3], also apparently because 2-phenyl-3-formyl-4H-chromene undergoes oxidative dehydration less readily than the pyran IIIa.

The pyrylium salt V reacted with ammonia and with benzylamine with retention of the aldehyde group, to give the hard to obtain 3-formylpyridine VI and the 3-formylpyridine salt VII. Retention of the aldehyde function in the reaction products VI and VII indicated that nucleophilic attack occurred at position 2 (but not 6) of the pyrylium cation, otherwise 3-benzoylpyrylium compounds XIV and XV would be obtained. The presence of the aldehyde group in compounds VI and VII, and also IIIa and IIIb, was confirmed by spectral methods (see Experimental) and by the "silver mirror" test. The regioselectivity of nucleophilic attack can be explained by the electron-withdrawing effect of the aldehyde group in the salt V, leading to an increase in the positive charge on the carbon atom at position 2 compared to that at position 6.

To study the possibility of ring fusion onto the pyrylium ring occurring, the aldehyde IX was synthesized; however, no cyclization products were obtained. The reaction of compound IX with perchloric or polyphosphoric acid or with tritylperchlorate gave only tarry products, probably due to polymerization at the allyl double bond. The use of methyltrifluoromethanesulfonate, which is known to attack exclusively electropositive atoms (but not carbon) [5], resulted in a salt-forming compound which proved to be pyrylium trifluoromethanesulfonate X. O-Methylation of the aldehyde group gave compound X, which then underwent a Koop rearrangement to give the intermediate XVI:



XVI

The driving force in the rearrangement, which took place irreversibly under relatively mild conditions (refluxing in dichloroethane), is the aromatization of the cation XVI to the pyrylium salt X. This was confirmed by the presence of a signal from the CH_3O group (3.14 ppm), suggesting that a methyltrifluoromethanesulfonate atom attacked the oxygen of the aldehyde function. The singlet at 8.73 ppm from the proton of the pyrylium cation, indicated that there was no allyl group at position 4 and, consequently, a rearrangement had occurred. With ammonium acetate, the salt X formed the corresponding pyridine XI, which gave no PMR signal at 8.73 ppm, so that for compound X this signal can be unambiguously assigned to the 4-H of the pyrylium cation.

This example of formylation has shown that electrophilic substitution of pyrans is a possibility. Further transformations of the 3-formylpyrans offer a method of preparing functionally substituted heterocyclic compounds that are otherwise difficult to prepare.

EXPERIMENTAL

IR spectra were taken on a Specord IR-71 using mineral oil (NaCl prism). PMR spectra were obtained on a Tesla BS-487C (80 MHz), internal standard HMDS.

Elemental analysis data were in agreement with calculated values.

2,4,6-Triphenyl-4H-pyran (IIa) was obtained by the method given in [6].

2,4,6-Triphenyl-3-methyl-4H-pyran (IIb, $C_{24}H_{20}O$). To a Grignard reagent prepared from magnesium (1.06 g, 44 mmoles) and bromobenzene (4.6 ml, 44 mmoles) in anhydrous ether (40 ml) was added 2,6-diphenyl-3-methylpyrylium perchlorate (7.7 g, 22 mmoles) [7]. When the pyrylium salt had dissolved, the excess organomagnesium compound was decomposed by the dropwise addition of saturated ammonium chloride solution. The ether layer was separated, dried with Na_2SO_4 and the solvent evaporated on the water bath. The remaining oil crystallized on standing in the refrigerator. The solid material was washed with pentane to give 6.82 g (87%) of IIb; mp 97–98°C. Compound IIb could not be recrystallized because of its high solubility in organic solvents. IR spectrum: 1690 and 1650 (C=C); 1595 cm^{-1} (C–C$_{ar}$). PMR spectrum (CCl_4): 1.45 (3H, s, CH_3); 3.88 (1H, d, 4-H); 5.29 (1H, d, 5-H); 6.8–7.8 ppm (15H, m, H$_{ar}$).

2,4,6-Triphenyl-3-formyl-4H-pyran (III, $C_{24}H_{18}O_2$) and 1,3,5-Triphenylpent-2-ene-1,5-dione (IV). To DMF (3.6 ml, 57 mmoles) in anhydrous methylene chloride (60 ml) was added phosphorus oxychloride (3.6 ml, 4 mmoles). After standing for 10 min, triphenyl-4H-pyran IIa (6.21 g, 2 mmoles) was added, and the mixture heated at reflux for 2 h. The reaction mixture was cooled by the addition of ice water and made alkaline by the dropwise addition of 30% aqueous NaOH solution. The organic layer was washed with water, and dried over Na_2SO_4. Evaporation of the solvent on the water bath gave a solid which was recrystallized from propyl alcohol (20 ml). Repeated recrystallization gave 5.28 g (78%) of compound IIIa; mp 145–147°C. IR spectrum: 1675 (CHO); 1647 (C=C); 1607 and 1593 cm^{-1} (C–C$_{ar}$). PMR spectrum ($CDCl_3$): 4.55 (1H, d, 4-H); 5.73 (1H, d, 5-H); 6.9–7.9 (15H, m, H$_{ar}$); 9.48 ppm (1H, s, CHO).

The cooled mother liquors from the first recrystallization of the aldehyde IIIa yielded a further 0.65 g (10%) of the diketone IV with mp 117°C (from ethanol); a sample gave no depression of the melting point when mixed with an authentic sample [8].

2,4,6-Triphenyl-3-formyl-5-methyl-4H-pyran (IIIb, $C_{25}H_{20}O_2$). To the pyran IIb (1.08 g, 3.3 mmoles) in anhydrous methylene chloride (5 ml) was added DMF (0.3 ml, 4.1 mmoles) and phosphorus oxychloride (0.31 ml, 3.4 mmoles). The mixture was refluxed for 3 h and the solvent evaporated on the water bath to give an oily residue which was washed several times with ether. Excess saturated K_2CO_3 solution was then added, and the material which separated was extracted with ether. Evaporation of the solvent and recrystallization of the residue from isopropyl alcohol afforded 0.70 g (60%) of a colorless crystal with mp 112–113°C. IR spectrum: 1693 (CHO); 1660 and 1613 (C=C); 1600 cm^{-1} (C–C$_{ar}$). PMR spectrum (CCl_4): 1.63 (3H, s, CH_3); 4.25 (1H, s, 4-H); 6.85–7.71 (15H, m, H$_{ar}$); 9.38 ppm (1H, s, CHO).

2,4,6-Triphenyl-3-formylpyrylium Perchlorate (V, $C_{24}H_{17}ClO_6$). A mixture of the aldehyde IIIa (3.38 g, 10 mmoles) and tritylperchlorate (3.43 g, 10 mmoles) in anhydrous nitromethane (25 ml) was refluxed for 1 h. After cooling, the reaction mixture was diluted with ether to give a precipitate of the salt V (3.7 g, 86%); mp 217–218°C (decomp.). IR spectrum: 1675 (CHO), 1610 (pyrylium cation), 1595 (C–C$_{ar}$), 1100 cm^{-1} (ClO_4^-). PMR spectrum (CD_3CN): 7.17–8.50 (15H, m, H$_{ar}$), 8.75 (1H, s, 5-H), 9.35 ppm (1H, s, CHO).

2,4,6-Triphenyl-3-formylpyridine (VI, $C_{24}H_{17}NO$). A mixture of the perchlorate V (0.44 g, 1 mmole) and ammonium acetate (0.3 g, 4 mmoles) in acetic acid (5 ml) was refluxed for 1 h 30 min. The mixture was then poured into water and extracted with ether. The ether solution was washed with Na_2CO_3 solution, dried with Na_2SO_4, and the solvent evaporated on the water bath. The residue was recrystallized from ethanol, to give 0.26 g (78%) of cream-colored needle-shaped crystals with mp 110°C. IR spectrum: 1647 (CHO), 1593 and 1580 cm^{-1} (C–C$_{ar}$). PMR spectrum (CCl_4): 6.9–8.2 (16H, m, H$_{ar}$ and 5-H), 8.62 ppm (1H, s, CHO).

N-Benzyl-2,4,6-triphenyl-3-formylpyridine Perchlorate (VII, $C_{31}H_{24}ClNO_5$). Benzylamine (0.1 ml, 1 mmole) was added to the perchlorate V (0.44 g, 1 mmole) in isopropyl alcohol (3.5 ml) and the mixture refluxed for 30 min. After cooling, excess ether was added and the colorless precipitate filtered off to yield 0.46 g (87%) of VII with mp 197–198°C. IR spectrum: 1670 (CHO), 1620 (pyridine cation), 1590 (C–C$_{ar}$), 1100 cm^{-1} (ClO_4^-). PMR spectrum (CD_3CN): 5.64 (2H, s, CH_2), 6.85–7.85 (15H, m, H$_{ar}$), 7.88 (1H, s, 5-H), 8.75 ppm (1H, s, CHO).

2,6-Diphenyl-3-methyl-4-allyl-4H-pyran (VIII, $C_{21}H_{20}O$). A suspension of allylmagnesium chloride [9], obtained from magnesium (0.8 g, 33 mmoles) and allyl chloride (2.5 ml, 33 mmoles) in anhydrous ether (15 ml) was cooled in an ice-water bath and 2,4,6-triphenyl-3-methylpyrylium perchlorate (3.48 g, 10 mmoles) added. When the pyrylium salt had dissolved, excess saturated aqueous ammonium chloride was added, the ether layer separated and dried with Na_2SO_4, and the solvent removed by distillation on the water bath. The remaining dark oily material was chromatographed on an alumina column (30 × 1.8 cm), and the fraction with R_f 0.5 collected; a benzene–hexane mixture (1:4) was used as eluent. The solvent was evaporated under vacuum on the water bath to give 2.07 g (72%) of an oily material. IR spectrum: 1693, 1660, and 1640 (C=C); 1600 and 1580 cm^{-1} (C–C_{ar}). PMR spectrum (CCl_4): 1.65 (3H, s, 3-CH_3), 2.08–2.53 (2H, m, –CH_2–), 2.78–3.10 (1H, m, 4-H), 4.83–5.20 (2H, m, =CH_2), 5.25 (1H, d, 5-H), 5.47–6.05 (1H, m, –CH=), 6.85–7.90 ppm (10H, m, H_{ar}).

2,6-Diphenyl-3-formyl-4-allyl-5-methyl-4H-pyran (IX, $C_{22}H_{20}O_2$). To a solution of DMF (0.85 ml, 12 mmoles) in methylene chloride (10 ml) was added phosphorus oxychloride (0.85 ml, 9.3 mmoles). Addition of this to the pyran VIII (1.35 g, 4.7 mmoles) gave a crimson coloration. The mixture was allowed to stand overnight and water (3 ml) and aqueous NaOH (5 ml, 30%) added. On warming, the color of the mixture lightened. The reaction products were extracted with ether, and the ether solution dried over Na_2SO_4. The solvent was distilled off on the water bath to give a red oil which was chromatographed on an alumina column (30 × 1.8 cm) using benzene as eluent. The fraction colored yellow was collected. A red impurity was left on the column. Evaporation of the benzene under reduced pressure on the water bath gave a yellow oil which crystallized on addition of hexane. Two recrystallizations from methanol gave 1.0 g (68%) of cream-colored crystals; mp 84–85°C. IR spectrum: 1680 (CHO), 1647 and 1613 (C=C), 1573 cm^{-1} (C–C_{ar}). PMR spectrum (CCl_4): 1.77 (3H, s, 5-CH_3), 2.20–2.50 (2H, m, –CH_2–), 3.35 (1H, t, 4-H), 4.80–5.15 (2H, m, =CH_2), 5.45–6.05 (1H, m, –CH=), 6.90–7.70 (10H, m, H_{ar}), 9.45 ppm (1H, s, CHO).

2,6-Diphenyl-3-(1-methoxybut-3-ene-1-yl)-5-methylpyrylium Trifluoromethanesulfonate (X). Methyltrifluoromethane sulfonate (0.25 ml, 1.5 mmoles) was added to a solution of compound IX (0.316 g, 1 mmole) in anhydrous dichloroethane (2 ml), and the solution refluxed for 1 h. After dilution with ether, the yellow material was filtered off to give 0.366 g (76%), mp 128–129°C (after reprecipitation from CH_2Cl_2 with ether). IR spectrum: 1640 (C=C), 1610 (pyrylium cation), 1590 (C–C_{ar}), 1250 ($CF_3SO_3^-$). PMR spectrum ($CDCl_3$): 2.33–2.76 and 2.60 (5H, m, –CH_2– and s, 5-CH_3, respectively*); 3.14 (3H, s, OCH_3), 4.40–4.68 (1H, m, CHOMe), 4.80–5.20 (2H, m, =CH_2), 5.43–6.00 (1H, m, –CH=), 7.10–8.08 (10H, m, H_{ar}), 8.73 ppm (1H, s, 4-H).

2,6-Diphenyl-3-(1-methoxybut-3-ene-1-yl)-5-methylpyridine (XI, $C_{23}H_{23}NO$). This was prepared in the same way as the pyridine VI from compound X (0.213 g, 0.65 mmole). It was purified by column chromatography on aluminum (10 × 2 cm), eluent 1:1 hexane–chloroform. Recrystallization from hexane gave 0.094 g (67%) of colorless crystals; mp 94–95°C. IR spectrum: 1640 (C=C), 1580 cm^{-1} (C–C_{ar}). PMR spectrum (CCl_4): 2.10–2.50 and 2.33 (5H, m, –CH_2– and s, 5-CH_3, respectively*), 3.00 (3H, s, OCH_3), 4.18–4.48 (1H, m, CH–OMe), 4.65–5.08 (2H, m, =CH_2), 5.33–5.90 (1H, m, –CH=), 7.00–7.67 ppm (11H, m, H_{ar} and 4-H).

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*The singlet from the 5-CH_3 group and the multiplet from the diastereotopic allyl group CH_2 are superimposed on each other.