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Vilsmeier–Haack reactions of carbonyl compounds: synthesis of substituted pyrones and pyridines

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Abstract—Vilsmeier–Haack reaction of substituted phenylacetones leads to the formation of conjugated iminium salts which on aqueous basic work up afford 3-formyl-4-pyrones and on ammonium acetate-induced cyclization afford 5-aryl-4-chloronicotinaldehydes in good yields.

1. Introduction

The Vilsmeier–Haack reaction is a widely used method for the formylation of activated aromatic and heteroaromatic compounds.[1,2] The reactions of aliphatic substrates,[3] particularly carbonyl compounds[4] with chloromethyleneiminium salts are highly versatile. They lead to multiple iminoalkylations in the presence of excess reagent and the resulting intermediates undergo cyclization to afford aromatic or heterocyclic compounds.[5,6] Multifunctional intermediates derived from these reactions (e.g., β-chloroenaldehydes) are subsequently exploited for the synthesis of functionalized heterocycles or other valuable target molecules.[7,8] Dibenzyl ketone on treatment with chloromethyleneiminium salt undergo multiple iminoalkylations followed by cyclization to afford 3,5-diphenyl-4*H*-pyran-4-one.[9,10] The reaction of *o*-hydroxyacetophenones with Vilsmeier-reagent also involve an iminoalkylation cyclization sequence, leading to the formation of 3-formyl chromones.[11–14]

We envisaged that methyl ketones having an additional enolizable methylene group at the α′ position should undergo multiple iminoalkylations on treatment with chloromethyleneiminium salt and the resultant intermediate on hydrolysis with saturated aq. potassium carbonate and subsequent cyclization should afford α-formyl-4-pyrones. Alternatively, cyclization of the multiple iminoalkylated intermediate induced by ammonium acetate prior to the work up would afford substituted pyridines. In this paper, we describe the reactions of some carbonyl compounds having two enolizable sp^2 or sp^3 hybridized carbons adjacent to the carbonyl group, and the cyclization reactions of the resulting iminoalkylated intermediates to substituted pyrones and pyridines.[15]

One of the general methods for the preparation of 4-pyrones involve cyclization of 1,3-dicarbonyl compounds obtained either by the addition of acyl ketenedithioacetals,[16] enamines[17] or enol ethers[18] to carboxylates or acid chlorides or by the addition of enamines to diketene.[19] Another approach towards the synthesis of 4-pyrones, particularly those having substituents at 2 and 6 positions, involve cyclization of 1,3,5-tricarbonyl compounds.[20–22] We have shown earlier that epoxidation of alkenoyl ketenedithioacetals followed by Lewis acid catalyzed rearrangement and cyclization leads to 2,5-disubstituted-4-pyrones.[23]

When benzyl methyl ketone was treated with 3 equiv. of the Vilsmeier–Haack reagent, prepared from DMF and $POCl_3$, for 72 h in DMF, 4-oxo-5-phenyl-4*H*-pyran-3-carbaldehyde **2a** was obtained in 59% yield (Scheme 1). Other substituted aryl acetones **1b-c** also reacted similarly to afford respective 3-formyl pyrones **2b-c**. We have recently shown that treatment of the multiple iminoalkylated intermediates derived from tertiary alcohols readily undergo cyclization in the presence of ammonium acetate to afford substituted pyridines.[24,25] We have therefore examined the reactivity of the intermediate iminium salt derived from aryl acetones towards similar cyclization. The reaction mixture after treatment of aryl acetones **1a** and **1c** with chloromethyleneiminium salt for 48 h at room temperature was cooled to 0–5 °C, and 40 equiv. of ammonium acetate was added and stirred for another 30 min, to afford the 5-aryl-4-chloro nicotinaldehydes **3a-b**.

Enolization of aryl acetones promoted in the presence of a

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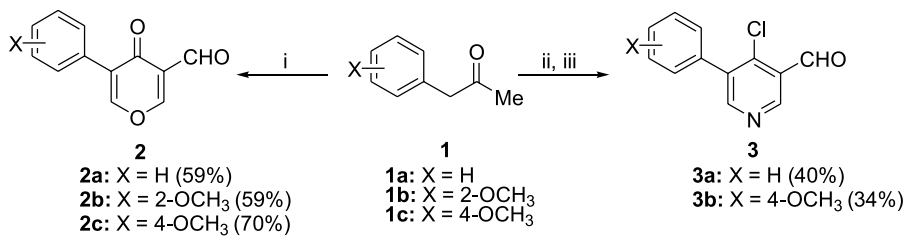
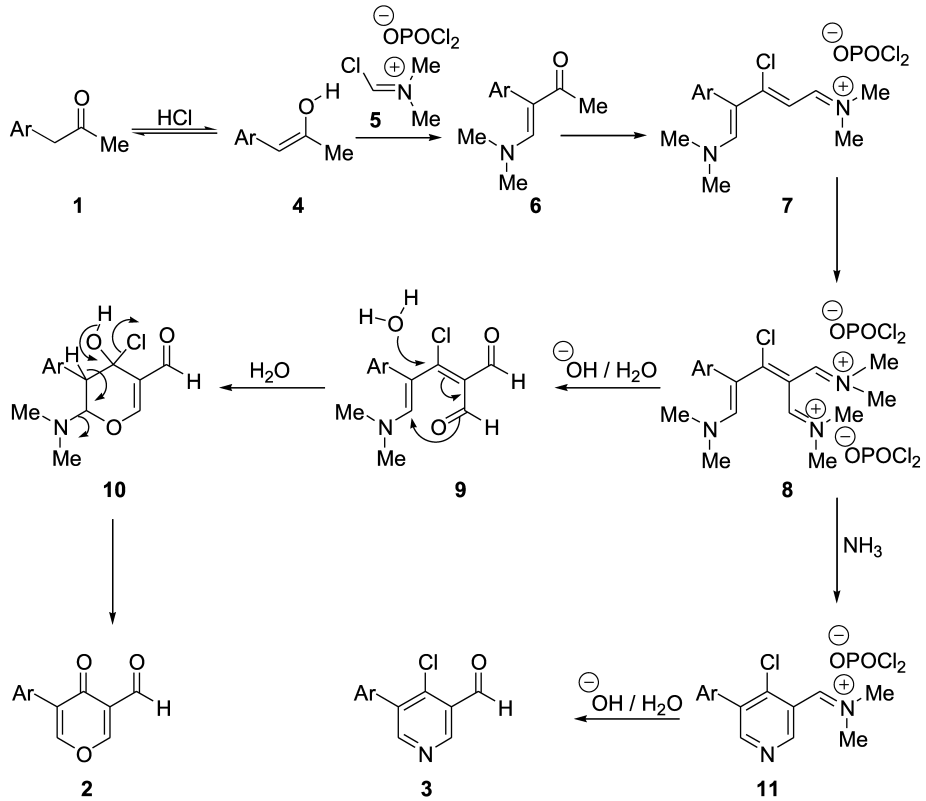


Scheme 1. Reagents and conditions: (i) DMF/$POCl_3$ (3 equiv.), 72 h, rt; (ii) DMF/$POCl_3$ (4 equiv.), 48 h, rt; (iii) NH_4OAc, 0 °C, 30 min.

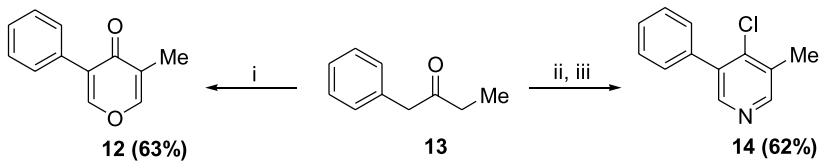
small amount of HCl followed by the addition of the enol to chloromethyleneiminium salt leads to the formation of the enaminoketone **6**. Sequential addition of this enaminoketone to 2 mol of chloromethyleneiminium salt results in the formation of the bis-iminium salt **8**. Hydrolysis of **8** should lead to the formation of the pentadienaldehyde **9** which undergo addition of a molecule of water followed by ring closure to afford an intermediate pyran **10**. Loss of HCl and dimethyl amine from **10** should lead to the formation of pyran-4-one **2**. Alternatively, cyclization of the intermediate bis-iminium salt **8** induced by ammonium acetate would give the iminium salt **11** which on aqueous work-up afford the substituted nicotinaldehydes **3** (Scheme 2).

Treatment of benzyl ethyl ketone **13** with the Vilsmeier–Haack reagent followed by hydrolysis gave the expected 3-methyl-5-phenyl-4*H*-pyran-4-one **12** in 63% yield. Alternatively, treatment of **13** with chloromethyleneiminium salt followed by ammonium acetate induced cyclization gave 4-chloro-3-methyl-5-phenylpyridine **14** in 62% yield (Scheme 3).

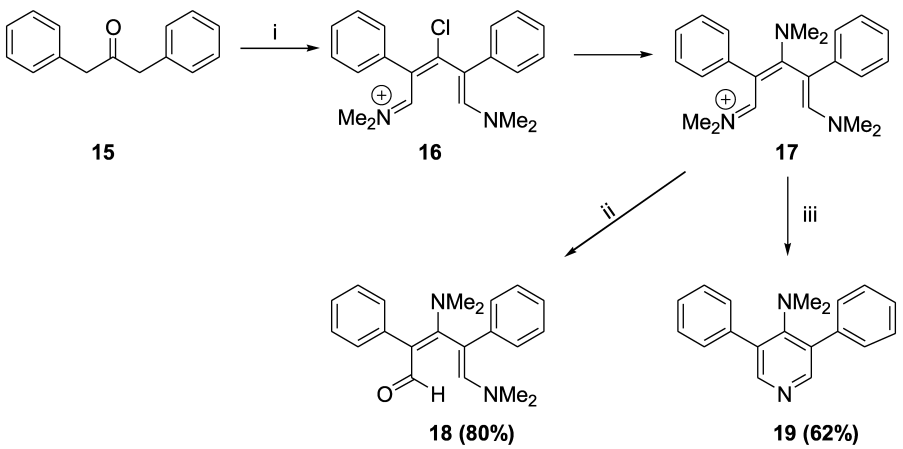
The formation of 3,5-diphenyl-4*H*-pyran-4-one from dibenzyl ketone on treatment with Vilsmeier reagent has been reported in the literature.[9,10] However, under our reaction conditions 3,5-bis(dimethylamino)-2,4-diphenyl-2,4-pentadienal **18** was formed as the only product in high



Scheme 2.



Scheme 3. Reagents and conditions: (i) DMF/$POCl_3$ (3 equiv.), 72 h, rt; (ii) DMF/$POCl_3$ (4 equiv.), 48 h, rt; (iii) NH_4OAc, 0 °C, 30 min.



Scheme 4. Reagents and conditions: (i) DMF/$POCl_3$ (3 equiv.), 72 h, rt; (ii) DMF/$POCl_3$ (4 equiv.), 48 h, rt; (iii) NH_4OAc, 0 °C, 30 min.

yield. It is interesting to note the introduction of *N*,*N*-dimethylamino substituent at the 3-position. Apparently, cyclization to the expected 4-pyrone is not favored by the presence of the dimethylamino group at the 3-position. However, the iminium salt **17** did undergo cyclization in the presence of ammonium acetate to afford 3,5-diphenyl-4-(*N*,*N*-dimethylamino)pyridine **19** (Scheme 4).

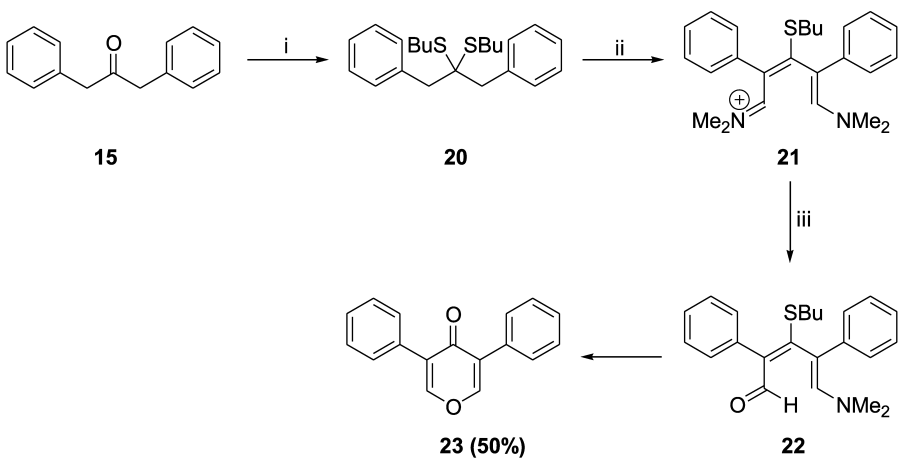
In a related experiment the dithioketal **20**, derived from the dibenzyl ketone **15** and butanethiol,[26] was subjected to Vilsmeier–Haack reaction in the presence of 3 equiv. of reagent prepared from $POCl_3$ and DMF for 16 h at room temperature. Subsequent basic hydrolysis gave 3,5-diphenyl-4*H*-pyran-4-one **23** in 50% yield. Obviously, **23** has been formed by the cyclization of the intermediate butylthio substituted pentadienaldehyde **22** (Scheme 5).

Phenoxyacetone **24** on treatment with Vilsmeier–Haack reagent followed by saturated aq. potassium carbonate gave 2[1-chloro-3-(dimethylamino)-2-phenoxy-2-propenylidene] malonaldehyde **26** as a pale yellow crystalline solid in 72% yield (Scheme 6). The fact that pentadienaldehyde **26**, formed by the hydrolysis of the bisiminium salt **25**, did not undergo further cyclization to give the expected 3-formyl pyrone **27** may be attributed to the reduced electrophilicity of C_5 of the pentadienaldehyde **26** due to the presence of the phenoxy substituent at C_4.

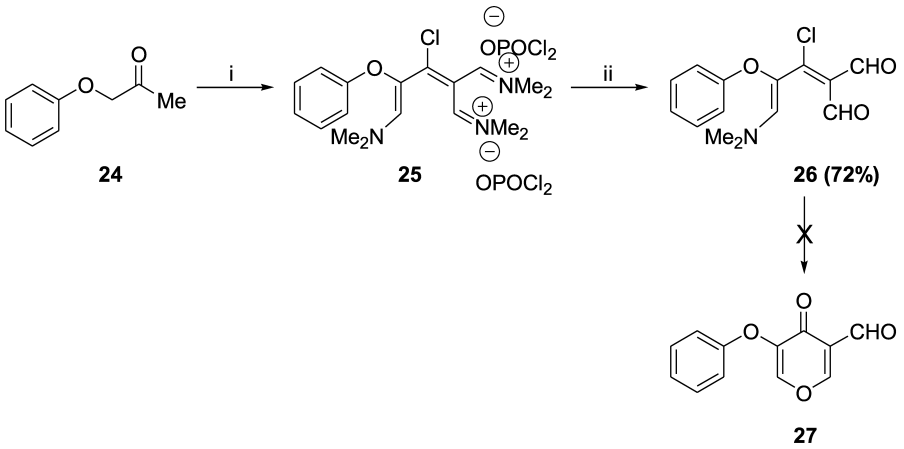
The reaction of benzylacetone **28** with Vilsmeier–Haack reagent under these conditions gave an unexpected product, 5-benzyl-4-hydroxy-6-(phenylethyl)isophthalaldehyde **33** in low yield among other unidentified products. The substituted phenol **33** must have resulted from the reaction of the α,β-unsaturated ketone **29**, which is the aldol type self-condensation product of benzylacetone, with chloromethyleneiminium salt. The bisiminium salt **30** formed by the multiple iminoalkylation of this ketone undergo cyclization and elimination of dimethylamine to afford the iminium salt **32** which on basic hydrolysis leads to the formation of **33** (Scheme 7). Similar cyclizations involving α,β-unsaturated ketones such as mesityloxide have been reported earlier.[27,28]

There are several approaches to the synthesis of 4-pyrones starting from but-3-ene-2-ones having an amino or alkoxy substituent at the 4-position.[17,29] The acyl ketenedithioacetals have alkylthio substituents at the β-position making them suitable candidates for the synthesis of 4-pyrones.[16] Against this background we have attempted to employ the Vilsmeier–Haack protocol for the synthesis of 4-pyrones starting from some substituted acyl ketenedithioacetals.

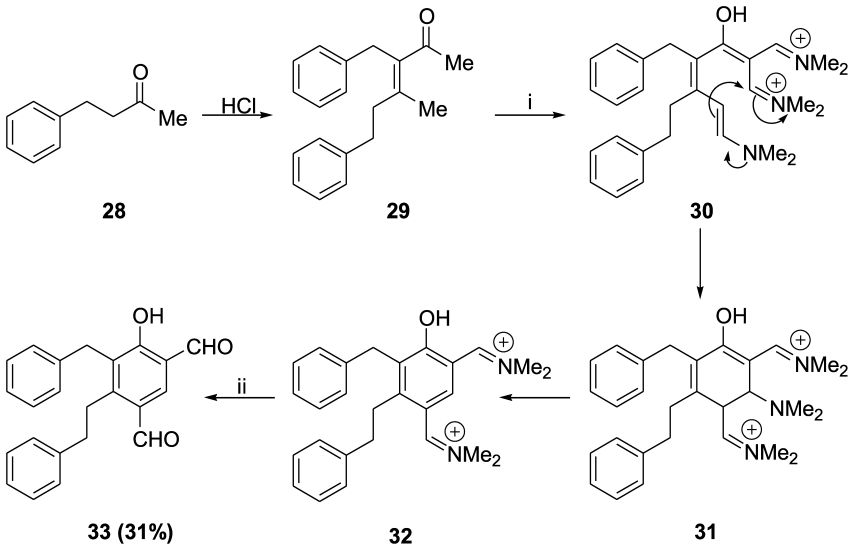
The ketenedithioacetal **36a** which was prepared from phenylacetone was allowed to react with 3 equiv. of Vilsmeier reagent for 72 h at room temperature. After the



Scheme 5. Reagents and conditions: (i) BuSH, $TiCl_4$, $CHCl_3$; (ii) DMF/$POCl_3$ (3 equiv.), 16 h, rt; (iii) $^-OH/H_2O$.



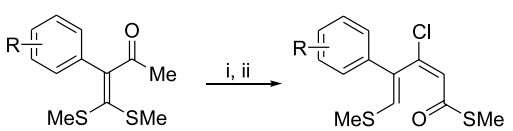
Scheme 6. Reagents and conditions: (i) DMF/$POCl_3$ (3 equiv.), 72 h, rt; (ii) $^{-}OH/H_2O$.



Scheme 7. Reagents and conditions: (i) DMF/$POCl_3$ (3 equiv.), 72 h, rt; (ii) $^{-}OH/H_2O$.

usual alkaline work up the S^1-methyl 3-chloro-5-(methylsulfanyl)-4-phenyl-2,4-pentadienethioate **37a** was isolated in 70% yield. Similarly *p*-methoxyphenyl substituted acyl ketenedithioacetal afforded the corresponding thiol ester **37b** (Scheme 8).

A plausible mechanism involving a 1,5-methylthio migration for the formation of the thiol ester **37** is depicted in Scheme 9. The initial iminoalkylation of the ketenedithioacetal leads to the formation of the iminium salt **38**. The presence of aryl substituent at the α-position of the ketenedithioacetal reduces the extent of delocalization of



36a: R = H
36b: R = 4-OCH_3

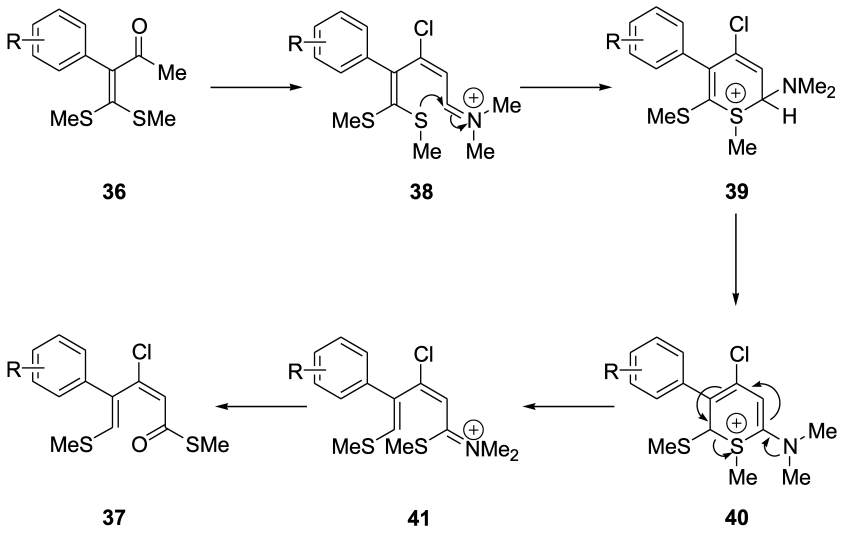
37a: R = H (70%)
37b: R = 4-OCH_3 (71%)

Scheme 8. Reagents and conditions: (i) DMF/$POCl_3$ (3 equiv.), 72 h, rt; (ii) $^{-}OH/H_2O$.

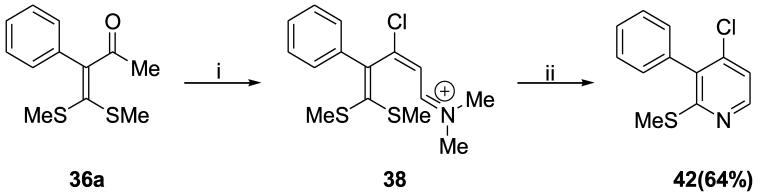
the carbonyl group from the ketenedithioacetal moiety. This favors enolization of the ketenedithioacetal **36** which is essential for the formation of iminium salt **38**. An intramolecular attack of the methylthio group to the iminium moiety results in the migration of the methylthio group which eventually lead to the formation of the iminium salt **41** which on hydrolysis gives the thiol ester **37**.

Treatment of the product mixture obtained by the addition of Vilsmeier reagent to the acyl ketenedithioacetal **36a** with excess ammonium acetate prior to the basic hydrolysis gave 4-chloro-2-(methylsulfanyl)-3-phenylpyridine **42** in 64% yield (Scheme 10). It is important to note that substituted nicotinaldehyde was not formed when ketenedithioacetal **36a** was used as the starting substrate, instead of phenylacetone. This could be attributed to the higher selectivity of ketenedithioacetals towards iminoalkylation compared to the corresponding enaminoketones which are the proposed intermediates involved in the direct reaction of ketones with chloromethyleneiminium salt.

In summary, we have shown that the Vilsmeier–Haack



Scheme 9.



Scheme 10. Reagents and conditions: (i) DMF/$POCl_3$ (3 equiv.), 72 h, rt; (ii) NH_4OAc, 0 °C, 30 min.

reactions of substituted phenylacetones followed by treatment with aq. K_2CO_3 or anhydrous NH_4OAc lead to the formation of 3-formyl-4-pyrones and 5-aryl-4-chloronicotinaldehydes, respectively, in good yields. The formation of 3-methyl-5-phenyl-4*H*-pyran-4-one and 4-chloro-3-methyl-5-phenylpyridine were observed in the case of benzyl ethyl ketone. However, other aliphatic ketones on treatment with the Vilsmeier reagent gave rather complex product mixtures. The reaction of phenoxyacetone and dibenzyl ketone did undergo multiple iminoalkylations under these conditions, but failed to give the expected pyran-4-one derivatives. But when the reaction was carried out using dibenzyl ketone followed by treatment with ammonium acetate 3,5-diphenyl-4-(*N*,*N*-dimethylamino)-pyridine was obtained instead of the corresponding chlorosubstituted pyridine. Nevertheless, the dithioketal of dibenzyl ketone gave 3,5-diphenyl-4*H*-pyran-4-one. We have also carried out some reactions on substituted ketenedithioacetals expecting the formation of substituted pyran-4-ones. Though the substituted ketenedithioacetals underwent Vilsmeier reaction smoothly, the product obtained were the substituted conjugated pentadiene thioicacid S-methyl esters on usual alkaline workup. However, on treatment with the Vilsmeier reagent followed by ammonium acetate, acyl ketenedithioacetal derived from phenylacetone afforded 4-chloro-2-(methylsulfanyl)-3-phenylpyridine.

2. Experimental

2.1. General

Melting points are uncorrected and were obtained on a Buchi-530 melting point apparatus. IR spectra were recorded on a Shimadzu IR-470 spectrometer. NMR spectra were recorded in deutereochloroform (internal standard TMS) on JEOL EX90 or Bruker WM200 or Bruker WM300 spectrometers; ^1H spectra at 90 or 200 or 300 MHz and ^{13}C spectra at 22.4 or 50.3 or 75.5 MHz, respectively, and coupling constants are given in Hz. Electron impact mass spectra were obtained on a Finnigan-MAT 312 spectrometer. Solvents were dried and distilled before use: *N*,*N*-dimethylformamide from $P_2O_5{\cdot}CHCl_3$ from anhydrous $CaCl_2$. Organic extracts were dried over anhydrous Na_2SO_4.

2.1.1. 4-Oxo-5-phenyl-4*H*-pyran-3-carbaldehyde (2a). Vilsmeier reagent was prepared by mixing ice-cold, dry DMF (50 mL) and $POCl_3$ (2.8 mL, 30 mmol). The mixture was then stirred for 15 min at room temperature. 1-Phenylacetone **1a** (1.34 g, 10 mmol) was dissolved in dry DMF (5 mL) and added over about 15 min at 0–5 °C. The reaction mixture was stirred for 72 h at room temperature. The mixture was then added to cold, saturated aq. K_2CO_3 (200 mL) and extracted with diethyl ether (3×50 mL). The organic layer was washed with water, dried over anhydrous Na_2SO_4, and evaporated to afford the crude product, which was column chromatographed over silica gel using hexane/ethyl acetate (9:1) as eluent to give the title compound **2a** (1.1 g, 59%), as a colorless crystalline solid, mp 148–149 °C. [Found: C, 71.92; H, 3.96. $C_{12}H_8O_3$ requires C, 72.0; H, 4.03%]; ν_{max}(KBr) 3020, 1700, (C=O), 1640, (C=O), 1540, 1320, 1270, 1010 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$): δ 7.10–7.80 (5H, m, arom. H), 7.90 (1H, s, vinylic), 8.40 (1H, s, vinylic), 10.35 (1H, s, CHO); ^{13}C NMR (22.64 MHz, $CDCl_3$): δ 124.32, 128.50, 129.00, 129.60, 132.55, 152.87, 159.20 (arom. and vinylic), 175.21

(C═O), 188.70 (C═O); EI-MS *m/z*: 200 (M^+), 172 (100%), 115 (50%), 102 (22%), 89 (11%).

2.1.2. 5-(2-Methoxyphenyl)-4-oxo-4*H*-pyran-3-carbaldehyde (2b). The title compound **2b** (1.1 g, 59%) a pale yellow crystalline solid, mp 127–129 °C was obtained by the same procedure as **2a** except using 1-(2-methoxyphenyl)acetone **1b** (1.64 g, 10 mmol) instead of **1a**. [Found: C, 67.75; H, 4.27. $C_{13}H_{10}O_4$ requires C, 67.82; H, 4.38%]; ν_{max}(KBr) 3015, 1685 (C═O), 1640 (C═O), 1600, 1540, 1485, 1455, 1305, 1285, 1260, 1240, 1080, 1020, 1005 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 3.80 (3H, s, OCH_3); 6.90–7.60 (4H, m, arom. H); 7.90 (1H, s, vinylic); 8.40 (1H, s, vinylic); 10.35 (1H, s, CHO); ^{13}C NMR (22.64 MHz, $CDCl_3$) δ 55.64 (OCH_3), 111.28, 118.74, 120.56, 124.17, 130.41, 130.52, 131.12, 154.30, 157.14, 159.17 (arom. and vinylic), 175.10 (C═O), 189.09 (C═O); EI-MS *m/z*: 230 (10%, M^+), 216 (20%), 202 (90%), 185 (21%), 159 (11%), 131 (66%), 115 (19%), 97 (18%), 85 (53%), 71 (56%).

2.1.3. 5-(4-Methoxyphenyl)-4-oxo-4*H*-pyran-3-carbaldehyde (2c). The title compound **2c** (1.61 g, 70%) a pale yellow crystalline solid, mp 153–154 °C was obtained by the same procedure as **2a** except using 1-(4-methoxyphenyl)acetone **1c** (1.64 g, 10 mmol) instead of **1a**. [Found: C, 67.76; H, 4.29. $C_{13}H_{10}O_4$ requires C, 67.82; H, 4.38%]; ν_{max}(KBr) 3060, 1685, (C═O), 1630, (C═O), 1600, 1535, 1500, 1350, 1320, 1290, 1275, 1250, 1180, 1100, 1030, 1015, 1005 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 3.8 (3H, s, OCH_3); 6.95 (2H, d, J=8 Hz, arom. H); 7.45 (2H, d, J=8 Hz, arom. H); 7.85 (1H, s, vinylic); 8.35 (1H, s, vinylic), 10.35 (1H, s, CHO); ^{13}C NMR (22.64 MHz, $CDCl_3$) δ 55.16 (OCH_3), 114.00, 121.78, 124.17, 129.72, 132.14, 152.18, 159.05 (arom. and vinylic), 160.24, 175.10 (C═O), 188.82 (C═O); EI-MS *m/z*: 230 (48%, M^+), 202 (100%), 187 (21%), 159 (15%), 145 (13%), 132 (17%), 117 (12%), 89 (19%).

2.1.4. 4-Chloro-5-phenylnicotinaldehyde (3a). Vilsmeier reagent was prepared by mixing ice-cold, dry DMF (50 mL) and $POCl_3$ (3.7 mL, 40 mmol). The mixture was then stirred for 15 min at room temperature. 1-Phenylacetone **1a** (1.34 g, 10 mmol) was dissolved in dry DMF (5 mL) and added over about 15 min at 0–5 °C. The reaction mixture was stirred for 48 h at room temperature and was cooled to 0–5 °C in an ice bath and excess solid ammonium acetate (40 equiv., 31 g) was slowly added to the reaction mixture and stirred for another 30 min. The mixture was then added to cold, saturated aq. K_2CO_3 (200 mL) and the white precipitate formed was filtered and dried. It was further purified by column chromatography over silicagel using hexane/ethylacetate (19:1) as eluent to give the title compound **3a** (1.74 g, 40%) as a white crystalline solid, mp 81–83 °C. [Found: C, 66.14; H, 3.68; N, 6.36. $C_{12}H_8ClNO$ requires C, 66.22; H, 3.70; N, 6.44%]; ν_{max}(KBr) 1690, 1550, 1430, 1380, 1305, 1260, 1070 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.27–7.50 (5H, m, arom.); 8.72 (1H, s, Py 6-H); 9.02 (1H, s, Py 2-H); 10.59 (1H, s, CHO); ^{13}C NMR (75.48 MHz, $CDCl_3$) δ 127.87, 128.60, 128.92, 129.48, 134.14, 137.40, 144.90, 149.63, 155.20 (arom.), 189.06 (CHO); EI-MS *m/z*: 219 (M^++2, 10%), 218 (M^++1, 33%), 217 (M^+, 30%) 216 (100%, M^+−1), 215 (64%), 198 (41%), 187 (33%), 152 (29%), 125 (53%), 77 (18%).

2.1.5. 4-Chloro-5-(4-methoxyphenyl)nicotinaldehyde (3b). The title compound **3b** (1.57 g, 34%, a white solid, mp 94–96 °C) was obtained by the same procedure as **3a** except using 1-(4-methoxyphenyl)acetone **1c** (1.64 g, 10 mmol) instead of **1a**. [Found: C, 62.91; H, 3.93; N, 5.57. $C_{13}H_{10}ClNO_2$ requires C, 63.04; H, 4.07; N, 5.66%]; ν_{max}(KBr) 1685, 1610, 1550, 1510, 1430, 1380, 1295, 1250, 1180, 1025 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.89 (s, 3H, OCH_3); 7.04 (d, 2H, J=8 Hz, arom.); 7.39 (, d, 2H, J=8 Hz, arom.); 8.64 (1H, s, Py 6-H); 9.17 (1H, s, Py 2-H); 10.59 (1H, s, CHO); EI-MS *m/z*: 249 (M^++2, 3%), 248 (M^++1, 33%), 247 (M^+, 10%) 246 (100%, M^+−1), 228 (83%), 140 (17%), 112 (18%).

2.1.6. 3-Methyl-5-phenyl-4*H*-pyran-4-one (12). The title compound **12** (1.45 g, 63%, a colorless crystalline solid, mp 90–92 °C) was obtained by the same procedure as **2a** except using 1-phenyl-2-butanone (1.48 g, 10 mmol) instead of **1a**. [Found: C, 77.36; H, 5.38. $C_{12}H_{10}O_2$ requires C, 77.40; H, 5.41%]; ν_{max}(KBr) 3010, 1640, 1610, 1490, 1410, 1330, 1290, 1040, 1000 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.0 (3H, s, CH_3); 7.2–7.9 (7H, m, arom. and vinylic); ^{13}C NMR δ (50.3 MHz, $CDCl_3$) 11.24 (CH_3), 126.28, 128.30, 128.41, 128.62, 128.80, 131.49, 151.24, 152.94 (arom. and vinylic), 177.50 (C═O); EI-MS *m/z*: 186 (100%, M^+), 129 (12%), 102 (84%), 89 (24%), 76 (19%).

2.1.7. 4-Chloro-3-methyl-5-phenylpyridine (14). Vilsmeier reagent was prepared by mixing ice-cold, dry DMF (50 mL) and $POCl_3$ (3.7 mL, 40 mmol). The mixture was then stirred for 15 min at room temperature. 1-Phenyl-2-butanone (1.48 g, 10 mmol) was dissolved in dry DMF (5 mL) and added over 15 min at 0–5 °C. The reaction mixture was stirred for 48 h at room temperature. It was then cooled to 0–5 °C in an ice bath and excess solid ammonium acetate (40 equiv., 31 g) was slowly added to the reaction mixture and stirred for another 30 min. The mixture was then added to cold, saturated aq. K_2CO_3 (200 mL) and extracted with diethyl ether (3×50 mL). The organic layer was washed with water, dried over anhydrous Na_2SO_4, and evaporated to afford the crude product, which was column chromatographed over silica gel using hexane/ethyl acetate (19:1) as eluent to give the title compound **14** (1.27 g, 62%) a brown viscous oil. [Found: C, 70.65; H, 4.88; N, 6.79. $C_{12}H_{10}ClN$ requires C, 70.77; H, 4.95; N, 6.88%]; ν_{max}(neat) 1550, 1450, 1400, 1270, 1230, 1170, 1070 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.45 (3H, s, CH_3), 7.39–7.44 (5H, m, arom.), 8.37 (1H, s, Py 6-H), 8.62 (1H, s, Py 2-H); ^{13}C NMR (75.48 MHz, $CDCl_3$) δ 17.91 (CH_3), 128.68, 128.73, 129.93, 130.01, 136.34, 142.97, 149.01; 149.11, 150.12; EI-MS *m/z*: 205 (M^++2, 8%), 204 (M^++1, 33%), 203 (M^+, 25%) 202 (100%, M^+−1), 201 (24%), 185 (46%), 167 (54%), 141 (41%), 115 (45%).

2.1.8. 3,5-Bis(dimethylamino)-2,4-diphenyl-2,4-pentadienal (18). To the Vilsmeier reagent prepared from $POCl_3$ (2.8 mL, 30 mmol) and dry DMF (50 mL) 1,3-diphenylacetone (2.1 g, 10 mmol) was added in dry DMF (5 mL) at 0–5 °C and the reaction mixture was stirred at room temperature for 72 h. It was then worked up using

cold, saturated aq. K_2CO_3 (200 mL) and extracted with diethyl ether (3×50 mL). The organic layer was washed with water, dried over anhydrous Na_2SO_4, and evaporated to afford the yellow crystals of the product, which was recrystallized from benzene to give the title compound **18** (2.56 g, 80%) a yellow crystalline solid, mp 140–142 °C. [Found: C, 78.68; H, 7.47; N, 8.63. $C_{21}H_{24}N_2O$ requires C, 78.72; H, 7.55; N, 8.74%]; ν_{max}(KBr) 2900, 1620 (C═O), 1580, 1380, 1285, 1085 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 2.4 (6H, s, $N(CH_3)_2$), 2.8 (6H, s, $N(CH_3)_2$), 6.8 (1H, s, vinylic), 7.0–7.5 (10H, m, arom.), 9.1 (1H, s, CHO); ^{13}C NMR (22.4 MHz, $CDCl_3$) δ 43.08 (CH_3), 43.50 (CH_3), 108.48, 121.22, 124.53, 125.30, 125.72, 127.51, 127.72, 128.29, 129.27, 129.96, 138.46, 138.70, 151.86, 173.84 (vinylic and arom.) 186.64 (CHO); EI-MS *m/z*: 320 (M^+, 35%), 303 (13%), 276 (54%), 202 (19%), 178 (11%), 145 (73%), 103 (21%), 89 (23%), 72 (98%).

2.1.9. 3,5-Diphenyl-4-(*N*,*N*-dimethylamino)pyridine (19). To the Vilsmeier reagent prepared from $POCl_3$ (3.7 mL, 40 mmol) and dry DMF (50 mL) 1,3-diphenylacetone (2.1 g, 10 mmol) was added in dry DMF (5 mL) at 0–5 °C and the reaction mixture was stirred at room temperature for 48 h. It was then cooled to 0–5 °C in ice and excess solid ammonium acetate (40 equiv., 31 g) was slowly added to the reaction mixture and stired for 30 min more. The mixture was then added to cold, saturated aq. K_2CO_3 (200 mL) and extracted with diethyl ether (3×50 mL). The organic layer was washed with water, dried over anhydrous Na_2SO_4, and evaporated to afford the product, which was column chromatographed over silicagel using hexane/ethylacetate (19:1) as eluent to give the title compound **19** (1.75 g, 62%) a brown viscous oil. [Found: C, 83.13; H, 6.57; N, 10.14. $C_{19}H_{18}N_2$ requires C, 83.18; H, 6.61; N, 10.21%]; ν_{max}(neat) 1580, 1510, 1435, 1420, 1310, 1230, 1135, 1070 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.24 (6H, s, $N(CH_3)_2$), 7.25–7.33 (10H, m, arom.), 8.19 (2H, s, Py, 2-H and 6-H); EI-MS *m/z*: 274 (100%, M^+), 273 (82%), 271 (21%), 259 (36%), 105 (59%), 91 (26%), 77 (30%).

2.1.10. 3,5-Diphenyl-4*H*-pyran-4-one (23). To the Vilsmeier reagent prepared from $POCl_3$ (2.8 mL, 30 mmol) and dry DMF (50 mL) dithioketal of 1,3-diphenylacetone (3.7 g, 10 mmol) was added in dry DMF (5 mL) at 0–5 °C and the reaction mixture was stirred at room temperature for 72 h. It was then worked up using cold, saturated aq. K_2CO_3 (200 mL) and extracted with diethyl ether (3×50 mL). The organic layer was washed with water, dried over anhydrous Na_2SO_4, and column chromatographed over silica gel using hexane/ethyl acetate (9:1) as eluent to give the title compound **23**. (1.3 g, 50%) a colorless crystalline solid, mp 185–186 °C (lit.,[10] 186–187 °C).

2.1.11. 2-[1-Chloro-3-(dimethylamino)-2-phenoxy-2-propenylidene]malonaldehyde (26). To the Vilsmeier reagent prepared from $POCl_3$ (2.8 mL, 30 mmol) and dry DMF (50 mL) 1-phenoxyacetone (1.5 g, 10 mmol) was added in dry DMF (5 mL) at 0–5 °C and the reaction mixture was stirred at room temperature for 72 h. It was then worked up using cold, saturated aq. K_2CO_3 (200 mL) and extracted with diethyl ether (3×50 mL). The organic layer was washed with water, dried over anhydrous Na_2SO_4, and evaporated to afford the yellow crystals of the product, which was recrystallized from benzene to give the title compound **26** (2 g, 72%) a pale yellow crystalline solid, mp 161–162 °C. [Found: C, 60.10; H, 4.92; N, 4.93. $C_{14}H_{14}ClNO_3$ requires C, 60.11; H, 5.04; N, 5.01%]; ν_{max}(KBr) 2980, 2700, 1720, 1680, 1580, 1480, 1400, 1260, 1250, 1210, 1180, 1130, 1010 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.25 (6H, s, $N(CH_3)_2$); 6.95–7.35 (6H, m, arom. and vinylic); 9.05 (1H, s, CHO), 9.45 (1H, s, CHO); ^{13}C NMR (75.48 MHz, $CDCl_3$) δ 39.81 (CH_3), 47.59 (CH_3), 115.21, 122.15, 129.66, 135.31, 147.51, 156.28, 160.11 (arom. and vinylic), 184.37 (CHO), 185.75 (CHO); EI-MS *m/z*: 281 (M^++2, 3) 279 (M^+, 12%), 278 (68%), 249 (27%), 186 (100%), 157 (38%), 94 (34%), 77 (56%).

2.1.12. 5-Benzyl-4-hydroxy-6-(phenylethyl)isophthalaldehyde (33). To the Vilsmeier reagent prepared from $POCl_3$ (2.8 mL, 30 mmol) and dry DMF (50 mL) 4-phenyl-2-butanone (1.48 g, 10 mmol) was added in dry DMF (5 mL) at 0–5 °C and the reaction mixture was stirred at room temperature for 72 h. It was then worked up using cold, saturated aq. K_2CO_3 (200 mL) and extracted with diethyl ether (3×50 mL). The organic layer was washed with water, dried over anhydrous Na_2SO_4, and column chromatographed using hexane/ethyl acetate (9:1) as eluent to give the title compound **33** (0.53 g, 31%) a colorless crystalline solid. [Found: C, 80.14; H, 5.79. $C_{23}H_{20}O_3$ requires C, 80.21; H, 5.85%]; ν_{max}(KBr) 1680, 1620, 1580, 1480, 1400, 1365, 1265, 1245, 1200, 1180, 1165, 1125, 1000 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.03 (2H, t, J=7 Hz, CH_2), 3.20 (2H, t, J=7 Hz, CH_2), 4.03 (2H, s, CH_2), 7.23–7.25 (10H, m, arom.), 7.99 (1H, m, OH), 8.06 (1H, m, arom.), 9.91 (1H, s, CHO), 11.73 (1H, s, CHO); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 30.29, 34.99, 40.15 (CH_2), 119.76, 126.29, 126.52, 128.46, 128.62, 128.64, 128.90, 129.11, 130.83, 132.93, 136.77, 139.19, 141.10, 163.27 (arom. and vinylic), 196.52, 196.78 (CHO); EI-MS *m/z*: 344 (44%, M^+), 239 (100%), 161 (28%), 91 (32%).

2.1.13. S[1]-Methyl 3-chloro-5-(methylsulfanyl)-4-phenyl-2,4-pentadienethioate (37a). To the Vilsmeier reagent prepared from $POCl_3$ (2.8 mL, 30 mmol) and dry DMF (50 mL) 4,4-bis(methylsulfanyl)-3-phenyl-3-buten-2-one **36a** (2.38 g, 10 mmol) was added in dry DMF (5 mL) at 0–5 °C and the reaction mixture was stirred at room temperature for 72 h. It was then worked up using cold, saturated aq. K_2CO_3 (200 mL) and extracted with diethyl ether (3×50 mL). The organic layer was washed with water, dried over anhydrous Na_2SO_4, and column chromatographed over silica gel using hexane/ethyl acetate (9:1) as eluent to give the title compound **37a** (1.98 g, 70%) a yellow crystalline solid, mp 97–98 °C. [Found: C, 54.78; H, 4.57. $C_{13}H_{13}ClOS_2$ requires C, 54.82; H, 4.60%]; ν_{max}(KBr) 1636 (C═O), 1555, 1520, 1480, 1430, 1310, 1260, 1220, 1080, 1045, 1025, 920, 845 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 2.2 (3H, s, SCH_3), 2.4 (3H, s, SCH_3), 7.0–7.8 (7H, m, arom. and vinylic); ^{13}C NMR (22.64 MHz, $CDCl_3$) δ 13.21 (SCH_3), 14.88 (SCH_3), 118.74, 127.96, 128.44, 130.79, 131.63, 136.43, 140.61, 141.21 (arom. and vinylic), 191.42 (C═O); EI-MS *m/z*: 284 (2%, M^+), 237 (100%), 189 (20%), 174 (46%), 115 (22%).

2.1.14. S[1]-Methyl 3-chloro-4-(4-methoxyphenyl)-5-(methyl-sulfanyl)-2,4-pentadienethioate (37b). The title

compound **37b** (2.24 g, 71%) a yellow crystalline solid, mp 97–99 °C was obtained by the same procedure as **37a** except using 3-(4-methoxyphenyl)-4,4-bis(methylsulfanyl)-3-buten-2-one **36b** (2.68 g, 10 mmol) instead of **36a**. [Found: C, 53.38; H, 4.76. $C_{14}H_{15}ClO_2S_2$ requires C, 53.41; H, 4.8%]; ν_{max}(KBr) 2900, 1630 (C=O), 1600, 1555, 1525, 1490, 1290, 1240, 1170, 1050, 1030, 925 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 2.2 (3H, s, SCH_3), 2.4 (3H, s, SCH_3), 3.85 (3H, s, OCH_3), 6.8–7.6 (6H, m, arom. and vinylic); ^{13}C NMR (22.64 MHz, $CDCl_3$) δ 13.27 (SCH_3), 14.85 (SCH_3), 55.01 (OCH_3), 113.37, 118.83, 128.53, 130.41, 131.36, 132.11, 140.49, 140.82, 159.67 (arom. and vinylic), 191.89 (C=O); EI-MS *m/z*: 316 (2%, M^++2), 314 (6%, M^+), 313 (14%), 266 (100%), 238 (17%), 223 (21%), 203 (78%), 188 (32%), 180 (18%), 160 (15%), 145 (45%).

2.1.15. 4-Chloro-2-(methylsulfanyl)-3-phenylpyridine (42). To the Vilsmeier reagent prepared from $POCl_3$ (2.8 mL, 30 mmol) and dry DMF (50 mL) 4,4-bis(methylsulfanyl)-3-phenyl-3-buten-2-one **36a** (2.38 g, 10 mmol) was added in dry DMF (5 mL) at 0–5 °C and the reaction mixture was stirred at room temperature for 72 h. It was then cooled to 0–5 °C in ice and solid ammonium acetate (40 equiv., 31 g) was slowly added to the reaction mixture in excess and stirred 30 min more. The reaction mixture was then worked up using cold, saturated aq. K_2CO_3 (200 mL) and extracted with diethyl ether (3×50 mL). The organic layer was washed with water, dried over anhydrous Na_2SO_4, and column chromatographed over silica gel using hexane as eluent to give the title compound **42** (1.5 g, 64%) a red liquid which turns to a purple colored liquid on solvent evaporation. [Found: C, 61.11; H, 4.21; N, 5.86. $C_{12}H_{10}ClNS$ requires C, 61.14; H, 4.28; N, 5.94%]; ν_{max}(neat) 2923, 1676, 1547, 1437, 1359, 1207 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.38 (3H, s, SCH_3); 7.05 (1H, d, *J*=5.5 Hz, Py 5-H); 7.17–7.21 (2H, m, Ph); 7.36–7.42 (3H, m, Ph); 8.24 (1H, d, *J*=5.5 Hz, Py 6-H); ^{13}C NMR (75.48 MHz, $CDCl_3$) δ 13.11 (SCH_3), 118.96, 127.67, 128.57, 132.91, 133.84, 141.36, 147.31, 160.18 (arom.); EI-MS *m/z*: 237 (M^++2, 8%), 236 (M^++1, 44%), 235 (M^+, 36%) 234 (100%, M^+−1), 233 (50%), 201 (58%), 200 (29%), 199 (50%), 154 (79%), 127 (24%), 105 (57%), 77 (43%).

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