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Reactions of 1-Aryl-2-propanones with Chloromethyleneiminium Salt

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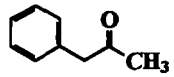
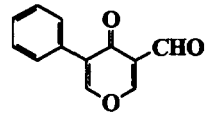
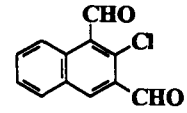
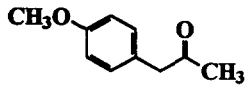
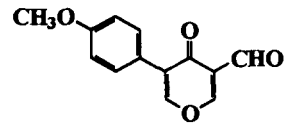
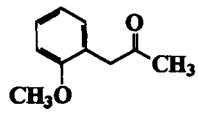
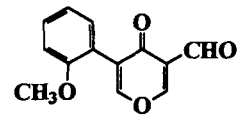
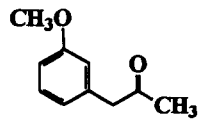
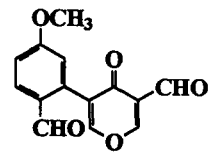
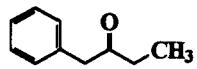
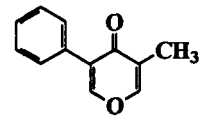
Abstract: A synthesis of 3-formyl-4-pyrones by Vilsmeier-Haack reaction of substituted benzyl methyl ketones has been reported. The reaction of benzyl ethyl ketone with chloromethyleneiminium salt gave corresponding 4-pyrone while phenoxy acetone gave N,N-dimethylamino substituted pentadienaldehyde. © 1997 Elsevier Science Ltd.

The reaction of chloromethyleneiminium salts with electron rich aromatic substrates provide one of the widely used method for formylation.[1] The carbon-carbon bond forming reactions of chloromethyleneiminium salts with aliphatic substrates, particularly carbonyl compounds containing methyl or methylene group adjacent to the carbonyl group are highly versatile.[2] The reaction often leads to products containing β-chlorovinyl aldehyde moieties. Ketones that possess methyl or methylene groups at both α-positions undergo multiple iminoalkylation reactions. This is exemplified by the reaction of dibenzyl ketone with Vilsmeier reagent to give 3,5-diphenyl-4-pyrone.[3] The reaction apparently proceeds by a double formylation and subsequent electrocyclic ring closure of the intermediate pentadienaldehyde to form a pyrylium salt. Though Vilsmeier reaction is widely used for the synthesis of 3-formyl chromones, examples of the synthesis of 3-formyl pyrones using a similar approach is not found in the literature.[4] Since dibenzyl ketone leads to the formation of 4-pyrone and *o*-hydroxy acetophenone affords 3-formyl chromone, benzyl methyl ketones appeared to be suitable substrates for the synthesis of 3-formyl pyrones. Here we report our results on the investigations of Vilsmeier reactions on α-substituted aliphatic ketones. The reaction proceeds with multiple iminoalkylations and cyclization to 3-formyl-4-pyrones are observed in the case of substituted aryl acetones. 1-Phenyl-2-butanone cyclized to the corresponding pyrone **11** under similar conditions. However phenoxy acetone gave the pentadienaldehyde **21** which did not undergo further cyclization under the reaction conditions.

Table: Synthesis of 3-formyl/unsubstituted 4-pyrones

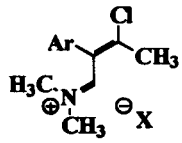
Entry	Substrate	Products[a] (Yield %)[b]	
1			
	1	2 (60)	3 (5)
2			
	4	5 (70)	
3			
	6	7 (63)	
4			
	8	9 (72)	
5			
	10	11 (59)	

[a] All products gave appropriate ^{1}H NMR, ^{13}C NMR, IR and mass spectra. [b] Isolated Yield

The reaction of phenyl acetone **1** with four equivalents of Vilsmeier reagent prepared from $POCl_3$ and DMF at room temperature for 72h[5] gave 5-phenyl pyran-4-one-3-carboxaldehyde **2**[6] in 60% yield along with small amounts of 3-chloronaphthalene1,3-dicarboxaldehyde **3**.[7] Similarly, other substituted 3-aryl-2-propanones also gave the corresponding 3-formyl 4-pyrones in good yields (table). However, the analogues of **3** could not be isolated from reactions of other substituted phenyl acetones. The reaction of 3-*m*-methoxy phenyl-2-propanone **8** was accompanied by formylation of the aromatic ring (table, *entry 4*). The reaction of

1-phenyl-2-butanone gave the 3-methyl-5-phenyl pyran-4-one **11** as the only isolated product in 59% yield (table, *entry 5*).

The reaction of benzyl methyl ketone with chloromethylene iminium salt is known to afford the chlorovinyl aldehyde **13** as mixture of stereoisomers.[8] This results from the hydrolysis of the intermediate chlorovinyl iminium salt **12**. The iminium salt **12** exists in equilibrium with the aminosubstituted diene **14** which on further iminoalkylation should give the iminium salt **15**. Subsequent iminoalkylation of **15** afford the bis iminium salt **16**. The pentadienaldehyde **17** could be formed by the hydrolysis of the iminium salt **16**. Cyclization of the pentadienaldehyde **17** to the pyran **18** and subsequent hydrolysis probably through an intermediate pyran **19** leads to the 5-aryl pyran-4-one-3-carboxaldehyde. The chlorosubstituted naphthalene dicarboxaldehyde **3** could be formed by cyclization of the iminium salt **16** (Ar = Ph) followed by subsequent hydrolysis.



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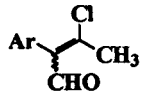

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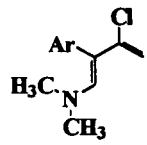

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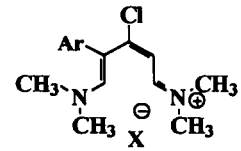

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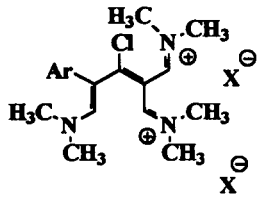
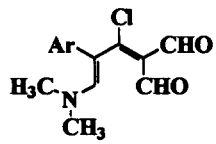


16



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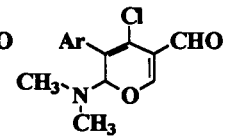

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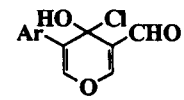

19

We have made further attempts to generalize this method for the synthesis of pyrones to other substituted aliphatic ketones. Simple aliphatic ketones usually gave complex mixtures and cycloaromatized products could be isolated in low yields. However phenoxy acetone **20** underwent a clean reaction and the product isolated in 72% yield was identified as the N,N-dimethylamino substituted pentadienaldehyde **21**[9] (Scheme 1). Apparently the presence of phenoxy group does not favour the cyclization to a pyrone. Further studies exploring the scope of this reaction in the synthesis of functionalized pyrones and their subsequent applications are in progress.

20 **21**

Scheme 1

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2. For an excellent review on the Vilsmeier reactions of carbonyl compounds see, Marson, C. M. *Tetrahedron*, **1992**, *48*, 3659.
3. Weissenfels, M.; Pulst, M.; Schnneider, P. *Z. Chem*, **1973**, *13*, 175.
4. Nohara, A.; Umetani, T.; Sanno, Y. *Tetrahedron Lett.*, **1973**, 1995.
5. *Typical procedure*: Vilsmeier-Haack reagent was prepared by mixing ice cold dry DMF (50mL) and $POCl_3$ (2.8 mL, 30 mmol). The mixture was then stirred for 15 minutes at room temperature. The ketone (10 mmol) was dissolved in dry DMF and added in about 15 minutes. The mixture was stirred for 72 hours at room temperature and then added to cold saturated K_2CO_3 solution (200 mL) and extracted with benzene (3x50 mL). The benzene layer was washed with water and dried over anhydrous Na_2SO_4 and evaporated to give the crude product. It was column chromatographed using hexane:ethyl acetate 9:1 as eluent.
6. *5-Phenylpyran-4-one-3-carboxaldehyde* **2**.mp. 148-149 ^{0}C ^{1}H NMRδ 7.1-7.8 (m, 5H, aromatic); 7.9 (s, 1H, vinylic); 8.4 (s, 1H, vinylic); 10.35 (s, 1H, CHO). ^{13}C NMR; (22.64 MHz, $CDCl_3$) δ 124.32(s), 128.50 (d), 129.00 (d),129.60 (s) 132.55 (s), 152.87(d), 159.20 (d), 175.21 (s), 188.70 (d). IR ν 1010, 1270, 1320, 1540, 1640, 1700, 3020. cm^{-1} EIMS m/z: 51 , 63 , 76 , 89 , 102 , 115 , 126 , 144 , 155 , 172 (100%), 200 (M^+).
7. *2-Chloronaphthalene-1,3-dicarboxaldehyde* **3** mp 110-112 ^{0}C ^{1}H NMR(95 MHz, $CDCl_3$) δ 7.50-8.10 (m, 3H, aromatic); 8.60 (s, 1H aromatic); 9.00 (d, J = 7 Hz, 1H, aromatic); 10.65 (s 1H. CHO); 10.95 (s, 1H, CHO); IR: ν_{max} 1450, 1660, 1710, 1750, 2860, 2920, 2965 cm^{-1} EIMS m/z 51, 63, 75, 86, 99, 126, 162, 189, 218 (100%, M^+)
8. Beaton, C. M.; Chapman, N. B.; Clarke, K.; Willis, J. M. *J. Chem. Soc., Perkin Trans. 1*, **1976**, 22, 2355.
9. *3-Chloro-5-N,N-dimethylamino-2-formyl-4-phenoxy-2,4-pentadienal* **21**. mp. 161-162 ^{0}C ^{1}H NMR: (300 MHz, $CDCl_3$) δ (ppm) 3.25 (s, 6H, $N(CH_3)_2$); 6.95-7.35 (m, 6H, aromatic and vinylic); 9.05 (s, 1H, CHO); 9.45 (s, 1H, CHO). ^{13}C NMR: (75.48 MHz, $CDCl_3$) δ (ppm) 39.81(q), 47.59(q), 115.21(d), 122.15(d), 129. 66(d), 135.31(s), 147.51, 156.28(s), 160.11(d), 184. 37(d), 185.75(d). IR ν_{max} 1010, 1130, 1180, 1210, 1250, 1260, 1400, 1480, 1580, 1680, 1720, 2700, 2980, 3480-3500 cm^{-1} EIMS: m/z 43, 77, 94, 157, 186 (100%), 249, 278 (M^+-1).

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