JOC Article

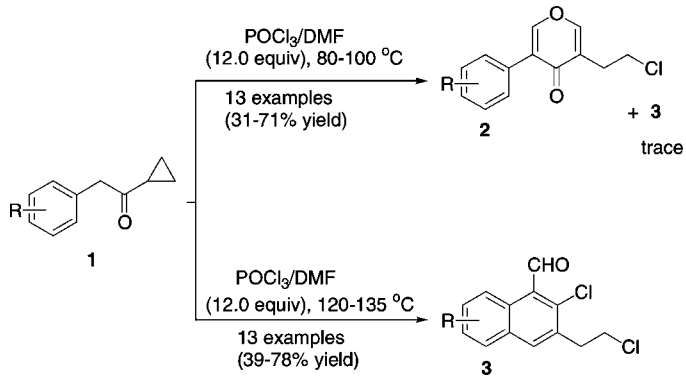
Vilsmeier−Haack Reaction of 1-Cyclopropyl-2-arylethanones

Xiang-Ying Tang and Min Shi*

State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, China

mshi@mail.sioc.ac.cn

Received July 7, 2008



A convenient and efficient method to synthesize 3-(2-chloroethyl)-5-aryl-4*H*-pyran-4-ones **2** and 2-chloro-3-(2-chloroethyl)-1-naphthaldehydes **3** in moderate to good yields was developed via the Vilsmeier−Haack reaction of readily available 1-cyclopropyl-2-arylethanones **1** at different temperature. This reaction proceeds via sequential enolization, ring opening, haloformylation, and intramolecular nucleophilic cyclization or Friedel−Crafts alkylation reactions to produce **2** or **3**.

Introduction

The halomethyleniminium salt derived from *N*,*N*-dimethylformamide (DMF) and phosphoryl chloride ($POCl_3$) is a potential intermediate involved in the Vilsmeier−Haack reaction.[1] The broad synthetic utility of this halomethyleniminium salt is not restricted to formylation but is also suitable for electrophilic substitutions followed by intramolecular cyclizations, producing various nitrogen and oxygen based heterocycles.[1] Among the versatile useful applications, the carbon−carbon bond-forming reactions of the Vilsmeier reagent with aliphatic substrates, particularly carbonyl compounds containing a methyl or methylene group adjacent to the carbonyl group, have been the interest of many organic chemists. Though the Vilsmeier−Hacck reaction is widely used and will continue to be an active and fruitful research area, there is a significant limitation because the weakly electrophilic Vilsmeier reagent reacts efficiently only with electron-rich aromatic systems.[2,3]

Cyclopropane-containing compounds, which can be used as versatile building blocks in organic synthesis, have been well understood for their well-known "unsaturated" character, which makes them readily go through a wide range of ring-opening reactions under the influence of many electrophilic and nucleophilic reagents. Previously, we reported $SnCl_4$ and TMSOTf mediated reactions of cyclopropyl alkyl ketones **1** with α-ketoesters and allenic esters as novel methods for the synthesis of 1,6-dioxaspiro[4.4]non-3-en-2-ones with high stereoselectivities, as well as dihydrofuro[2,3-*h*]chromen-2-one and 2,3-dihydrobenzofuran-4-ol derivatives in moderate to good yields under mild conditions.[4] As 1-cyclopropyl-2-arylethanones **1** contain a methylene group and

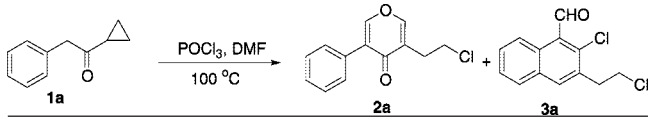
(1) (a) Vilsmeier, A.; Haack, A. *Ber. Dtsch. Chem. Ges.* **1927**, *60*, 119. (b) Jutz, C. *Adv. Org. Chem.* **1976**, *9*, 225–342. (c) Seshadri, S. J. *Sci. Ind. Res.* **1973**, *32*, 128–149. (d) Jones, G.; Stanforth, S. P. *Org. React.* **2000**, *56*, 355–659. (e) Marson, C. M. *Tetrahedron* **1992**, *48*, 3659–3726. (f) Meth-Cohn, O. *Heterocycles* **1993**, *35*, 539–557. (g) Perumal, P. T. *Indian J. Heterocycl. Chem.* **2001**, *11*, 1–8. (h) Pan, W.; Dong, D.-W.; Liu, Q. *Org. Lett.* **2007**, *9*, 2421–2423. (i) Wang, K.-W.; Xiang, D.-X.; Dong, D.-W. *Org. Lett.* **2008**, *10*, 1691–1694.

(2) For reviews on the Vilsmeier−Haack Reaction, see: (a) Jutz, C. *Adv. Org. Chem.* **1976**, *9*, 225. (b) Meth-Cohn, O.; Tarnowski, B. *Adv. Heterocycl. Chem.* **1982**, *31*, 207. (c) Meth-Cohn, O.; Stanforth, S. P. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 2, p 777. (d) de Maheas, M.-R. *Bull. Soc. Chim. Fr.* **1962**, 1989. (e) Minkin, V. I.; Dorofeenko, G. N. *Russ. Chem. Rev.* **1960**, *29*, 599.

(3) (a) Nirmala, K. N.; Asokan, C. V. *Tetrahedron Lett.* **1997**, *38*, 8391. (b) Thomas, A. D.; Asokan, C. V. *Tetrahedron* **2004**, *60*, 5069. (c) Arindam, C.; Jayanta, K. R. *Synth. Commun.* **1995**, *25*, 1869. (d) Lebedev, A. V.; Lebedeva, A. B.; Sheludyakov, V. D.; Kovaleva, E. A.; Ustinova, O. L.; Kozhevnikov, I. B. *Russ. J. Gen. Chem.* **2005**, *75*, 412. (e) Weissenfels, M.; Pulst, M.; Cao, W.; Riedel, D.; Greif, D. *Molecules* **1996**, *1*, 264.

10.1021/jo801492k CCC: $40.75 © 2008 American Chemical Society
Published on Web 09/26/2008

TABLE 1. Reaction of 1-Cyclopropyl-2-phenylethanone (1a) with Vilsmeier Reagent under Various Reaction Conditions



entry[a]	$POCl_3$ (equiv)	t (min)	yield (%)[b] 2a	3a
1	5	60	30	*d*
2	10	20	68	*d*
3	15	20	46	11
4	12	20	71	*d*
5	12	10	31	*d*
6	12	40	40	20
7	12	60	37	25
8	12	40	57[c]	*d*

[a] All reactions were performed with **1a** (0.3 mmol) and DMF (3 mL). [b] Isolated yield. [c] Reaction was conducted at 80 °C. [d] Cannot be isolated by flash column chromatography.

a cyclopropane adjacent to the carbonyl group, we envisaged that treatment of these substrates with dehydrating reagents might lead to interesting transformations.[5] Experiments along these lines did not look promising until we treated **1** with the Vilsmeier reagent. As a result, we found a convenient and efficient method for the synthesis of substituted pyranones **2** and naphthaldehydes **3**, respectively, by carrying out the Vilsmeier−Haack reaction of readily available **1** at different temperatures. In this paper, we wish to report our findings in this area. To the best of our knowledge, this is the first report that these substrates, which have an electron-withdrawing group on the benzene ring, can undergo Vilsmeier-type reaction.

Results and Discussion

We initially chose 1-cyclopropyl-2-phenylethanone **1a** as a model to investigate its reaction behavior upon heating with the Vilsmeier reagent ($POCl_3$/DMF, 5.0 equiv) under different conditions. Treatment of **1a** with the Vilsmeier reagent at 100 °C for 1 h afforded 3-(2-chloroethyl)-5-phenyl-4*H*-pyran-4-one **2a** as a yellow liquid along with trace of naphthaldehyde **3a** and the recovery of starting materials **1a** in 30% within 1 h (Table 1, entry 1). To our delight, increasing the amount of the Vilsmeier reagent to 10.0 equiv produced **2a** in 68% yield along with a trace of **3a** and the complete conversion of **1a** after 20 min (Table 1, entry 2). Further investigations were aimed at determining the optimal conditions by changing the ratio of the Vilsmeier reagent and **1a**, as well as altering the reaction time. The results of these experiments are summarized in entries 3−8 in Table 1. As can be seen in Table 1, in the presence of a large excess amount of the Vilsmeier reagent (15.0 equiv), **2a** was obtained in a much lower yield of 46% along with the formation of naphthaldehyde **3a** in 11% yield (Table 1, entry 3). However, using 12.0 equiv of $POCl_3$/DMF under identical conditions afforded **2a** in 71% yield (Table 1, entry 4). Further investigation of the reaction time revealed that increasing or decreasing the reaction time did not improve the yields of **2a** and that the optimal reaction time was 20 min (Table 1, entries 5−7). For example, when the reaction time was prolonged to 40 and 60 min, product **2a** was obtained in 40% and 37% yields along with the formation of **3a** in 20% and 25% yields, respectively (Table 1, entries 6 and 7). In addition, **2a** was obtained in 57% yield when the reaction was performed at 80 °C under otherwise identical conditions (Table 1, entry 8). In all the cases shown in Table 1, **3a** was formed as a minor product.

SCHEME 1. Vilsmeier−Haack Reaction of 1a at 110 and 120 °C

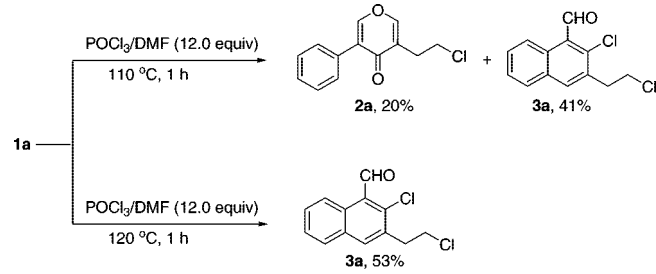
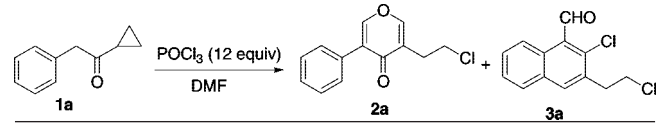


TABLE 2. Summary of Temperature Effect



entry	T (°C)	yield (%)[a] 2a	3a
1	100	71	*b*
2	110	20	41
3	120	0	53
4	135	0	46

[a] Isolated yields. [b] Cannot be isolated by flash column chromatography.

Next, we attempted to obtain compound **3a** as a sole product. By raising the reaction temperature to 110 °C, both **2a** and **3a** were obtained in 20% and 41% yields, respectively (Scheme 1). When the reaction of **1a** with the Vilsmeier reagent (12.0 equiv) was performed at 120 °C, we found that **3a** was formed in 53% yield without the formation of **2a**, suggesting that **3a** could be formed as a sole product at higher temperature (Scheme 1). The summary of the temperature effect on this reaction is in Table 2. It is clear that the temperature can significantly affect the reaction outcomes. The optimal temperature for the formation of **3** was 120 °C. Upon treatment of another substrate 1-cyclopropyl-2-(3-methoxyphenyl)ethanone **1k** with the Vilsmeier reagent under the same conditions, compound **3k**, an analog of **3a**, was obtained, and its structure was unambiguously confirmed by the X-ray single crystal analysis, the CIF data of which are presented in Supporting Information.[6]

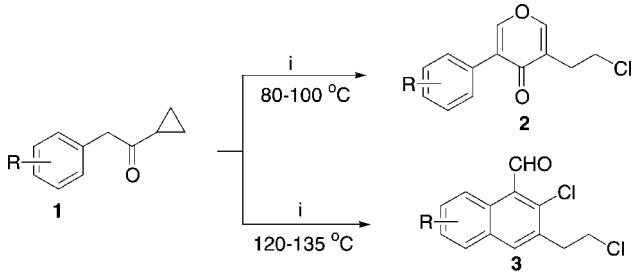
Having these optimized reaction conditions in hand, we next attempted to determine the reaction generality. However, we found that upon treatment of 2-(4-chlorophenyl)-1-cyclopropylethanone **1b** and 1-cyclopropyl-2-(3-methoxyphenyl)ethanone **1k** with the Vilsmeier reagent (12.0 equiv) at 100 and 120 °C, to our surprise, the reaction consequences were quite different. Using **1b** as the substrate afforded **2b** as a major product along with a trace of **3b** at 100 °C, but both **2b** and **3b** were obtained in 24% and 41% yields at 120 °C, respectively. Using **1k** as the substrate afforded **3k** as a sole product despite changing

(4) (a) Yang, Y.-H.; Shi, M. *Org. Lett.* **2006**, *8*, 1709–1712. (b) Shi, M.; Tang, X.-Y.; Yang, Y.-H. *Org. Lett.* **2007**, *9*, 4017.

(5) It was found that compound **1a** decomposed after 1 h upon treatment with DMF/$(COCl)_2$ or PBr_3/CBr_4 at 100 °C.

(6) The crystal data of **3k** have been deposited in CCDC with number 662441. Empirical formula, $C_{14}H_{12}O_2Cl_2$; formula weight, 283.14; crystal size, 0.483 × 0.301 × 0.190; crystal color, habit, colorless, prismatic; crystal system, triclinic; lattice type, primitive; lattice parameters, a = 4.4303(9) Å, b = 10.037(2) Å, c = 14.798(3) Å, α = 87.946(4)°, β = 87.265(4)°, γ = 79.808(3)°, V = 646.7(2) Å^3; space group, *P*-1; Z = 2; D_{calc} = 1.454 g/cm^3; F_{000} = 292; $R1$ = 0.0449, $wR2$ = 0.1207. Diffractometer: Rigaku AFC7R.

TABLE 3. Vilsmeier−Haack Reaction of Various 1-Cyclopropyl-2-arylethanones



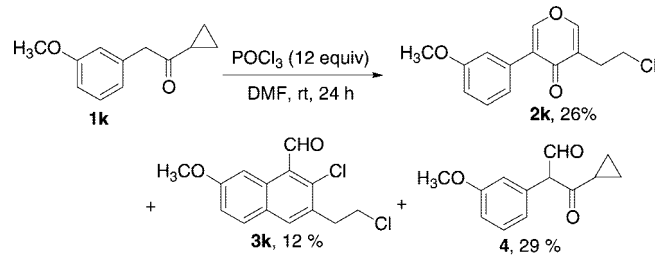
entry[a]	R	*T* (°C)	yield, **2**[c] or **3** (%)[b]
1	**1b**, *p*-CI	100	**2b**, 44
		135	**3b**, 42
2	**1c**, *p*-Br	100	**2c**, 43
		135	**3c**, 39
3	**1d**, *m*-Br	100	**2d**, 45
		135	**3d**, 67[d]
4	**1e**, *p*-F	100	**2e**, 65
		135	**3e**, 75
5	**1f**, *m*-F	100	**2f**, 51
		135	**3f**, 60[d]
6	**1g**, *o*-Br	100	**2g**, 31
		135	**3g**, *f*
7	**1h**, *p*-Me	100	**2h**, 52
		120	**3h**, 40
8	**1i**, *p*-MeO	100	**2i**, 61
		120	**3i**, *f*
9	**1j**, *o*-MeO	100	**2j**, 51[e]
		120	**3j**, 0[e]
10	**1k**, *m*-MeO	80	**2k**, 69
		120	**3k**, 78
11	**1l**, *m*-Me	100	**2l**, 59
		120	**3l**, 74
12	**1m**, *o*-Me	100	**2m**, 48[e]
		120	**3m**, 0[e]
13	**1n**, -C_4H_4- (α-naphthyl)	100	complex
		120	**3n**, 88

[a] Reaction conditions: (i) $POCl_3$/DMF (12.0 equiv); 20 min. [b] Isolated yields. [c] Trace ot **3** was formed in most cases. [d] A pair of isomeric mixtures was obtained (see Supporting Intormation). [e] The product **3** was not formed. [f] Cannot be isolated by flash column chromatography.

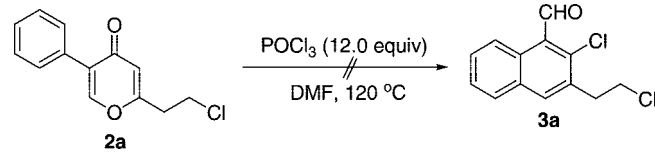
the temperature from 100 to 120 °C without the formation of **2k**. On the basis of these results, we realized that the electron-withdrawing group or electron-donating group on the benzene ring of the substrates significantly affected the Vilsmeier−Haack reaction outcomes as a result of the weak electrophilicity of the Vilsmeier reagent. Ror substrates having electron-donating groups on the benzene ring, the Vilsmeier−Haack reaction can proceed much more easily under identical conditions. On the other hand, for substrates bearing electron-withdrawing groups on the benzene ring, higher reaction temperature is required.

Accordingly we continued to determine the scope and limitations of these reactions. Thus, a series of 1-cyclopropyl-2-arylethanones **1b**−**1g** having an electron-withdrawing group on the benzene ring were subjected to the Vilsmeier reagent (12.0 equiv) at 100 and 135 °C, respectively.[7] The corresponding 4*H*-pyranone derivatives **2b**−**2g** were obtained in moderate yields along with traces of **3b**−**3g** (Table 3, entries 1−6) at 100 °C, and the corresponding naphthaldehyde derivatives **3b**−**3g** were obtained as the sole products in moderate yields in most cases at 135 °C (Table 3, entries 1−6). Only in the case of substrate **1g** bearing an *ortho* Br atom on the benzene ring, a trace of **3g** was obtained, presumably due to the electronic effect and steric hindrance (Table 3, entry 6).[8] In the case of substrates **1h** and **1i**, the corresponding 4*H*-pyranone derivatives **2h** and **2i** were formed in 52% and 61% yields at 100 °C and the yield of **3h** was 40%, but only a trace of **3i** was formed at 135 °C (Table 3, entries 7 and 8).[8] Moreover, for substrates **1k** and **1l** bearing a strongly electron-donating methoxy group and a moderately electron-donating methyl group in the *meta* position of the benzene ring, the reactions proceeded much more smoothly to afford the corresponding 4*H*-pyranone derivatives **2k** and **2l** in 69% and 59% yields along with traces of **3k** and **3l** at 80 and 100 °C, respectively (Table 3, entries 10 and 11). Moreover, naphthaldehyde derivatives **3k** and **3l** were formed in moderate yields at 120 °C as the sole products (Table 3, entries 10 and 11). For substrates **1j** and **1m**, bearing a strongly electron-donating methoxy group and a moderately electron-donating methyl group in the *ortho* position of the benzene ring, the corresponding 4*H*-pyranone derivatives **2j** and **2m** were formed in 51% and 48% yields at 100 °C, respectively. However, the corresponding naphthaldehyde derivatives **3j** and **3m** were not formed under the standard conditions, presumably due to the electronic effect and steric hindrance (Table 3, entries 9 and 12).[8] In the case of 1-cyclopropyl-2-naphthylethanone **1n**, complex product mixtures were formed at 100 °C, while raising the reaction temperature to 120 °C afforded the corresponding naphthaldehyde **3n** in 68% yield (Table 3, entry 13).

SCHEME 2. Vilsmeier−Haack Reaction of 1-Cyclopropyl-2-(3-methoxyphenyl)ethanone 1k at Room Temperature



SCHEME 3. Treatment of 2a with Vilsmeier Reagent at 120 °C



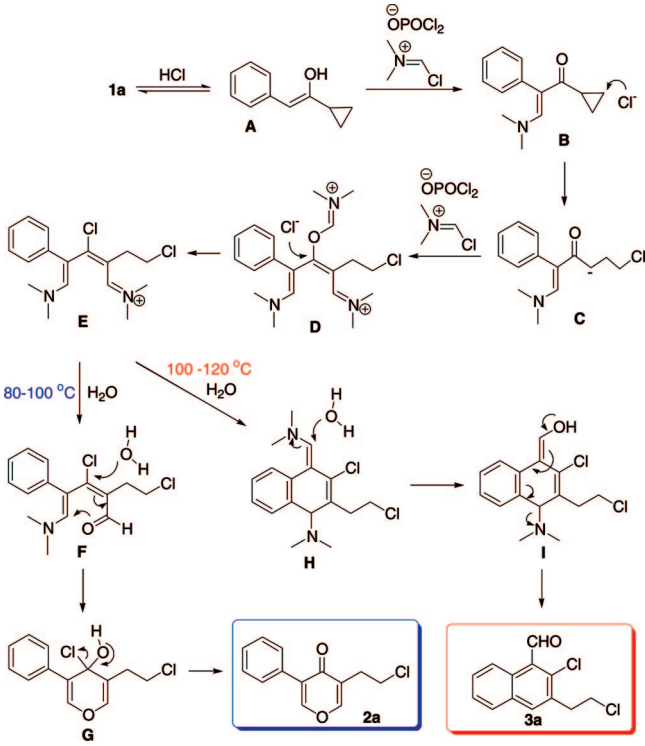
To gain more mechanistic insights into this interesting ring-opening/cyclization reaction, two control experiments were conducted under the standard reaction conditions. Upon treatment of **1k** with the Vilsmeier reagent ($POCl_3$/DMF, 12.0 equiv) at room temperature for 24 h followed by quench of the reaction with the addition of water, we found that products **2k**, **3k**, and **4** were obtained in 26%, 12%, and 29% yields, respectively (Scheme 2). In addition, no reaction occurred when **2a** was subjected to the Vilsmeier reagent ($POCl_3$/DMF, 12.0 equiv) at 120 °C, suggesting that naphthaldehyde derivative **3** is not derived from 4*H*-pyranone derivative **2** under the reaction conditions; in other words, naphthaldehyde **3** is the thermodynamically more stable product and product **4** might be the intermediate in this reaction (Scheme 3).

On the basis of above results and previous literature,[3a,b] a plausible mechanism for the formation of **2** and **3** is outlined in

(7) For these substrates having electron-withdrawing group on the benzene ring, the Vilsmeier−Hacck reaction should be conducted at 135 °C to produce a clean product.

(8) The reasons why none of naphthaldehyde derivatives **3j** and **3m** and a trace of **3g** and **3i** were formed will be explained later in this paper.

SCHEME 4. Plausible Reaction Mechanism



Scheme 4 using **1a** as a model. At first, **1a** is easily transformed into its enol intermediate **A** with hydrochloric acid produced by the Vilsmeier reagent, which is alkylated to give a *N*,*N*-dimethylaminovinyl ketone **B** that undergoes a subsequent ring-opening reaction by chloride ion to generate enolate **C**. This reactive intermediate **C** further reacts with the Vilsmeier reagent to give a biiminium salt intermediate **D**, which undergoes a nucleophilic replacement by chloride ion to form intermediate **E**. This is the key intermediate in this transformation. When the reaction temperature is 80−100 °C, intermediate **E** is mainly hydrolyzed by water to give intermediate **F**, which produces intermediate **G** through cyclization along with the elimination of dimethylamine. Dehydrochlorination of intermediate **G** furnishes 4*H*-pyranone product **2a**. On the other hand, when the reaction is performed at higher temperature (120 °C or at 135 °C for other substrates), intermediate **E** can generate a new hexatomic ring via an intramolecular Friedel−Crafts reaction to form intermediate **H**. Hydrolysis of intermediate **H** by water affords intermediate **I**, which gives naphthaldehyde **3a** after elimination of dimethylamine. It should be also noted that intermediate **E** can also be partially transformed into intermediate **H** when the reaction is carried out at 80 or 100 °C, affording naphthaldehyde **3a** in low yield, particularly if the reaction time is prolonged. This is why trace of **3** was obtained along with the formation of **2** as shown in Tables 1 and 2, although **2a** can not be transformed to **3a** under the reaction conditions.

Now we can explain why naphthaldehydes **3j** and **3m** were not formed upon treatment of **1j** and **1m** with the Vilsmeier reagent under the standard conditions. According to the substituent effects, the electron-donating group facilitates the electrophilic substitution at the *ortho* and *para* position of the benzene ring rather than the *meta* position, and thus the intramolecular Friedel−Crafts reaction at the *meta* position of the *o*-methoxy or *o*-methyl group does not take place. What is more, the steric effects of *ortho* substituents are also significant since in these cases, the corresponding products **3** are not formed. For the same reason, trace of **3i** is obtained because of the *p*-methoxy group deactivated its *meta*-position and the Friedel−Crafts reaction is difficult. Meanwhile, trace of **3g** is formed due to that half of the position to form the hexatomic ring via intramolecular Friedel−Crafts reaction is occupied by electron-withdrawing *ortho*-Br atom in **1g**, which does not facilitate such electrophilic substitution either. This is also why in the reactions of **1** bearing an electron-withdrawing group on the benzene ring with the Vilsmeier reagent, the higher reaction temperature is required.

In summary, a convenient and efficient method for the synthesis of 3-(2-chloroethyl)-5-aryl-4*H*-pyran-4-ones **2** and 2-chloro-3-(2-chloroethyl)-1-naphthaldehydes **3** was developed from the Vilsmeier−Haack reaction of cyclopropyl alkyl ketones **1**, which involves sequential enolization, ring-opening, haloformylation, and intramolecular nucleophilic cyclization or Friedel−Crafts alkylation reactions. This synthetic protocol is associated with readily available starting materials, a structurally wide range of products, and easy control of the reaction conditions. The potential utilization and extension of the scope of the methodology are currently under investigation.

Experimental Section

General Procedure for the Reaction of 2a and 3a. The Vilsmeier reagent was prepared by adding $POCl_3$ (4.5 mmol) dropwise to ice-cold dry DMF (2 mL) under stirring. After 10 min, to the above Vilsmeier reagent was added 1-cyclopropyl-2-phenylethanone **1a** (48 mg, 0.3 mmol) as a solution in DMF (1.0 mL). The reaction mixture was stirred at 100 °C (120 °C/135 °C) for 20 min. Then the mixture was poured into ice-cold water (20 mL) and extracted with dichloromethane (3 × 20 mL), and the combined organic phases were washed with water (3 × 20 mL), dried over $MgSO_4$, and filtered. The organic layer was removed under reduced pressure, and then the residue was purified by flash column chromatography.

3-(2-Chloroethyl)-5-phenyl-4*H*-pyran-4-one (2a). A yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz, TMS) δ 2.87 (t, J = 6.0 Hz, 2H, CH_2), 3.81 (t, J = 6.0 Hz, 2H, CH_2), 7.38−7.46 (m, 3H, Ar), 7.50−7.53 (m, 2H, Ar), 7.80 (s, 1H), 7.91 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz, TMS) δ 29.6, 42.6, 125.6, 128.4, 128.7, 129.0, 131.0, 152.9, 153.0, 176.6; IR (CH_2Cl_2) ν 3082, 2964, 2924, 1646, 1616, 1493, 1448, 1281, 1192, 1047 cm^{-1}; MS (EI) *m*/*z* (%) 234 [M$^+$] (12.3), 235 (7.0), 200 (15.9), 199 (100), 119 (6.8), 115 (7.3), 102 (16.0), 89 (8.8); HRMS (EI) calcd for $C_{13}H_{11}O_2Cl$ (M$^+$) requires 234.0448, found 234.0457.

2-Chloro-3-(2-chloroethyl)-1-naphthaldehyde (3a). A yellow solid. Mp 68−70 °C. ^{1}H NMR ($CDCl_3$, 300 MHz, TMS) δ 3.40 (t, J = 6.6 Hz, 2H, CH_2), 3.86 (t, J = 6.6 Hz, 2H, CH_2), 7.55 (t, J = 7.2 Hz, 1H, Ar), 7.64 (td, J = 7.2 Hz, J = 0.9 Hz, 1H, Ar), 7.82 (d, J = 7.8 Hz, 1H, Ar), 7.96 (s, 1H, Ar), 8.98 (d, J = 9.0 Hz, 1H, Ar), 10.9 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz, TMS) δ 36.7, 43.0, 124.5, 127.2, 128.0, 128.1, 129.5, 130.4, 131.8, 133.1, 136.2, 140.1, 192.9; IR (CH_2Cl_2) ν 3058, 2925, 2853, 1690, 1589, 1495, 1454, 1377, 1261, 1069 cm^{-1}; MS (EI) *m*/*z* (%) 252 [M$^+$] (20.7), 203 (42.2), 79 (100), 175 (25.3), 152 (25.9), 151 (42.9), 139 (21.4), 41 (35.8). Anal. Calcd. for $C_{13}H_{10}Cl_2O$: C, 61.68; H, 3.98. Found: C, 61.41; H, 4.11.

Acknowledgment. We thank the Shanghai Municipal Committee of Science and Technology (04JC14083, 06XD14005), and the National Natural Science Foundation of China (20472096, 203900502, 20672127, and 20732008).

Supporting Information Available: Spectroscopic data (^{1}H, ^{13}C spectroscopic data), HRMS of the compounds shown in Tables 1 and 2, X-ray crystal structure of compound **3k** in CIF format, and detailed description of experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

JO801492K