Note

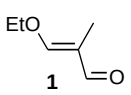
# Direct Formylation of Enol Ethers Using Cyanuric Chloride and *N*,*N*-Dimethylformamide

Duen-Ren Hou[1]* ( 侯敦仁 ), Chong-Si Sun ( 孫崇喜 ), Wu-Sian Sie ( 謝武憲 ), Jing-Yu Jian ( 簡靜瑜 ) and Yun Hsu ( 徐　昀 )
*Department of Applied Chemistry, National University of Kaohsiung, 700 Kaohsiung University Road, Kaohsiung City, 811, Taiwan, R.O.C.*

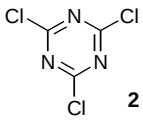
A new method to prepare α,β-unsaturated enol aldehydes is described. 3-Ethoxymethacrolein (**1**) and 5-formyl-3,4-dihydro-2*H*-pyran (**5**) were effectively prepared from enol ethers and the Vilsmeier-Haack type complex, derived from cyanuric chloride and DMF. One byproduct, amidine **4**, was also characterized.

**Key words:** Formylation; Enol ether; α,β-Unsaturated aldehyde; Vilsmeier-Haack complex.

α,β-Unsaturated enol aldehydes, such as 3-ethoxymethacrolein (**1**), are useful precursors to heterocyclic compounds.[2] Breitmaier's group developed a multi-step synthesis to 2-methyl malonic dialdehyde tetraethylacetal, then hydrolyzed to give the compound **1**.[2] Nair et al. have reported the Vilsmeier formylation of propionaldehyde diethyl acetal in the presence of *N*,*N*-dimethylformamide (DMF) and phosphorous oxychloride ($POCl_3$) to give the ethoxymethacrolein in 26% yield.[3] Although this method provides a quick entrance to the compound **1**, the evolution of gaseous HCl and the difficult work-up/purification procedures are problematic. Babler's group also reported the crossed-Claisen condensation of methyl formate and propanal to give the compound **1** in 61% yield after the alkylation with ethyl bromide.[4] However, this long procedure and the extremely moisture sensitive reaction condition also limit its application. Therefore, developing a direct method to prepare **1** could be useful.




**1**

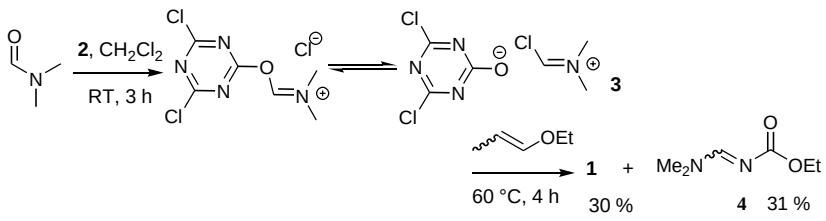



**2**

The application of cyanuric chloride (**2**) has drawn attention recently.[5-9] Cyanuric chloride, a white solid at room temperature, is commercially available, inexpensive and easy to handle, which makes it an ideal reagent for the chlorination of alcohols.[5,8] In addition, the formate protection of various alcohols using the combination of cyanuric chloride and DMF has also been reported.[6] The active intermediate in these reactions, the Vilsmeier-Haack type complex (**3**),[10-14] implied the possible application to the formylation of enol ethers. Herein, we report our study in preparing the α,β-unsaturated enol aldehydes from enol ethers and cyanuric chloride/DMF.

As shown in Scheme I, the Vilsmeier type complex was prepared by mixing cyanuric chloride with DMF in dichloromethane at room temperature for 3 h.[6] Then the ethyl propenyl ether was added to the reaction and gently refluxed (60 °C, oil bath) for another 4 h. The reaction was basified with $K_2CO_{3(aq)}$, extracted, dried and concentrated to give an oily, crude product. The aldehyde **1** was then harvested with flash column chromatography, or vacuum distillation (22-30% yield). During our search to improve the yield, we found that unlike Nair's synthesis, 2-methyl-3-(dimethylamino)prop-

**Scheme I**

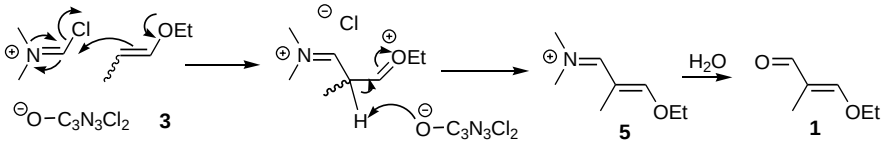


2-enal was not formed in this reaction.[3] Instead, an amidine byproduct **4** was isolated (31% yield). The proposed reaction mechanism to account for the formation of **1** and **4** is shown in Schemes II and III, respectively. The key precursor to the aldehyde **1**, the iminium enol **5**, comes from the substitution and deprotonation of enol ether with the complex **3**. On the other hand, the formation of **4** is intriguing since it is constituted with ethoxy, *N*,*N*-dimethylformamidine and carbamic acid ester. Evidently, these three components come from ethyl propenyl ether, DMF and cyanuric chloride. Although the detailed mechanism to form **4** is not clear at this moment, the linkage between the carbamic carbon and the dimethylformamidine suggests the existence of other ionic complexes, such as **6**. The presence of the carbamic acid ethyl ester also indicates the decomposition of enol ether to release ethanol (Scheme III). This competitive process significantly reduces the yield of the desired aldehyde **1**. Although the isolated yield is similar to that using Nair's method, this reaction generates much less $HCl_{(g)}$ and its work-up is easier than the reaction using phosphorous oxychloride.

To further examine the scope of this reaction, other enol ethers were also tested. The results are summarized in Table 1. 2,3-Dihydropyran gives the corresponding aldehydes **8** in 25% yield. The aldehyde **9** from the formylation of 2,3-dihydrofuran is contaminated with other impurities and has a poor yield. In addition to the competitive pathway shown above, this low yield is also due to the liability of the aldehyde **9**.[15] For the reaction of *n*-butyl vinyl ether, we were disappointed to find that this reaction only gives a complex, unidentified mixture, which thwarts further purification. This tar-like product was examined with mass spectroscopy directly. Indeed, the corresponding mass of **10** was found, and its high-resolution mass analysis also matched the composition of the aldehyde **10**. We believe that the formylation of this terminal alkene also occurs, but the product may undergo further reactions due to the presence of α-acidic proton in **10**.

In conclusion, we have developed a short, easy and economical synthesis to 3-ethoxymethacrolein using ethyl propenyl ether and cyanuric chloride/DMF. This methodology may also apply to preparation of other α,β-unsaturated enol

**Scheme II**




**Scheme III** The proposed mechanism to **4**

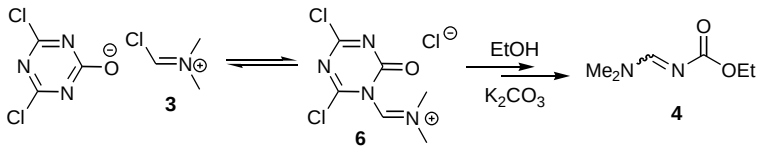
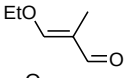
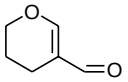
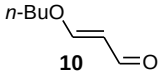



Table 1. Formation of α,β-Unsaturated Enol Aldehydes

| Entry | enol | product | reaction temp. | reaction time (h) | Yield (%) |
|---|---|---|---|---|---|
| 1 |  |  | 60 °C | 4 | 22 |
| 2 |  |  **8** | 25 °C | 48 | 25 |
| 3 |  |  **9** | 25 °C | 48 | 5 |
| 4 |  |  **10** | 25 °C | 48 | – |

aldehydes.

## EXPERIMENTAL SECTION

### General

$CH_2Cl_2$ was distilled from $CaH_2$; DMF was dried over 4 Å molecular sieves. All other chemicals were purchased from Aldrich or Arcos Organics and used without further purification. $^1H$ and $^{13}C$ NMR spectra were obtained on Varian 200 or 300 MHz spectrometers and referenced to TMS or residual $CHCl_3$. Analytical TLC was carried out using Merck aluminum-backed 0.2 mm silica gel 60 F254 plates. Column chromatography was conducted using Merck silica gel 60 (230-400 mesh).

### 3-Ethoxymethacrolein (1)

Cyanuric chloride (7.7 g, 41.8 mmol) suspended in DMF (3.6 mL, 46 mmol) and $CH_2Cl_2$ (10 mL) was stirred at room temperature for 3 h. Ethyl propenyl ether (3.0 g, 34.8 mmol) was added to the slurry, and the reaction was gently refluxed in a 60 °C oil bath for another 4 h. The reaction was cooled to 0 °C, and sat. $K_2CO_{3(aq)}$ (40 mL) was poured into the reaction. The reaction mixture was further diluted with water (20 mL), $CH_2Cl_2$ (50 mL) and stirred for 1 h. The precipitate was removed by filtration, then the organic layer was separated, and the aqueous solution was further extracted with $CH_2Cl_2$ (25 mL × 2). The combined organic solution was washed with water (20 mL), sat. $NaCl_{(aq)}$ (20 mL), dried over $Na_2SO_{4(s)}$, and concentrated to give the crude oily product. The crude product was further purified with column chromatography (silica gel, ethyl acetate/*n*-hexane = 1/1(v/v), $R_f$ = 0.58) to give a colorless oil of **1** (0.86 g, 22%). $^1H$ NMR ($CDCl_3$, 200 MHz) δ 9.19 (s, 1H), 6.95 (s, 1H), 4.15 (q, *J* = 7.4 Hz, 2H), 1.64 (s, 3H), 1.36 (t, *J* = 7.4 Hz, 3H). $^{13}C$ NMR ($CDCl_3$, 50.3 MHz) δ 191.6, 167.6, 119.9, 70.9, 15.3, 6.3. The spectroscopy data were consistent with those reported by Nair et al.[3] The crude product could also be distilled under vacuum (0.3 torr) to give **1** (b.p. 42-45 °C, 1.1 g, 30%) and the dimethylformamidine **4** (b.p. 75-80 °C, 1.55 g, 31%) as colorless oil. The spectroscopy data of **4**: $^1H$ NMR ($CDCl_3$, 300 MHz) δ 8.40 (s, 1H), 4.15 (q, *J* = 7.0 Hz, 2H), 3.08 (s, 3H), 3.03 (s, 3H), 1.26 (t, *J* = 7.0 Hz, 3H). IR (neat) 2981, 2359, 1670, 1619, 1432, 1340, 1240, 1060 $cm^{-1}$; $^{13}C$ NMR ($CDCl_3$, 75.5 MHz) δ 164.3, 162.8, 61.3, 41.2, 35.1, 14.3. MS (FAB): 145 ($M + H^+$), 99, 73, 44. HRMS (ESI): calcd for $C_6H_{13}N_2O_2$, 145.0972, found 145.0973. The reported $^1H$ NMR chemical shift of $Me_2NC\mathbf{H}$=NCOOR: δ 8.64.[16]

### 5-Formyl-3,4-dihydro-2*H*-pyran (5)

Cyanuric chloride (7.0 g, 38.0 mmol) suspended in DMF (3.6 mL, 46 mmol) and $CH_2Cl_2$ (10 mL) was stirred at room temperature for 3 h. 3,4-Dihydro-2H-pyran (3.0 g, 35.6 mmol) was added to the slurry, and the reaction was stirred at room temperature for another 48 h. The reaction was cooled to 0 °C, and sat. $K_2CO_{3(aq)}$ (20 mL) was poured into the reaction. The reaction mixture was further diluted with water (20 mL), $CH_2Cl_2$ (50 mL) and stirred for 1 h. The precipitate was removed by filtration, the organic layer was separated, and the aqueous solution was further extracted with $CH_2Cl_2$ (25 mL × 2). The combined organic solution was washed with water (20 mL), sat. $NaCl_{(aq)}$ (20 mL), dried over $Na_2SO_{4(s)}$, and concentrated to give the crude oily product. The crude product was further purified with column chromatography (silica gel, ethyl acetate/*n*-hexane = 3/7(v/v), $R_f$ = 0.29) to give a colorless oil of **5** (1.0 g, 25%). $^1H$ NMR ($CDCl_3$, 300 MHz) δ 9.10 (s, 1H), 7.26 (s, 1H), 4.14 (t, *J* = 5.4 Hz, 2H), 2.20 (t, *J* = 6.3 Hz, 2H), 1.84 (m, 2H). $^{13}C$ NMR ($CDCl_3$, 75.5 MHz) δ 190.4, 165.1, 119.3, 68.3, 20.4, 16.5. The spectroscopy data were consistent with those reported previously.[17]

### 3-Formyl-4,5-dihydro-furan (9)

Cyanuric chloride (3.5 g, 19.0 mmol) suspended in DMF (1.8 mL, 23 mmol) and $CH_2Cl_2$ (5 mL) was stirred at room temperature for 3 h. 4,5-Dihydro-furan (1.2 g, 17.0 mmol) was added to the slurry, and the reaction was stirred in a 0 °C ice-water bath for another 18 h. Sat. $K_2CO_{3(aq)}$ (15 mL) and water (15 mL) were poured into the reaction. The reaction mixture was extracted with $CH_2Cl_2$ (20 mL × 3). The combined organic solution was washed with water (20 mL), sat. $NaCl_{(aq)}$ (20 mL), dried over $Na_2SO_{4(s)}$, and concentrated to give the crude oily product. The crude product can be partially purified with column chromatography (silica gel, ethyl acetate/*n*-hexane = 3/7(v/v), $R_f$ = 0.28) to give the compound **9** (0.08 g, 5%). $^1H$ NMR ($CDCl_3$, 300 MHz) δ 9.65 (s, 1H), 7.32 (t, *J* = 1.2 Hz, 1H), 4.66 (t, *J* = 9.6 Hz, 2H), 2.87 (dt, *J* = 9.6 Hz, *J* = 1.2 Hz, 2H). MS (EI) *m/z*: 98. The spectroscopy data were consistent with those reported previously.[15]

### Formylation of n-butyl vinyl ether

Cyanuric chloride (0.42 g, 2.3 mmol) suspended in DMF (165 μL, 2.1 mmol) and $CH_2Cl_2$ (1 mL) was stirred at room temperature for 3 h. n-Butyl vinyl ether (191 mg, 1.9 mmol) was added to the slurry, and the reaction was stirred for another 48 h at room temperature. Sat. $K_2CO_{3(aq)}$ (2 mL) and water (2 mL) were poured into the reaction. The reaction mixture was extracted with $CH_2Cl_2$ (5 mL × 3). The combined

organic solution was washed with water (3 mL), sat. $NaCl_{(aq)}$ (3 mL), dried over $Na_2SO_{4(s)}$, and concentrated to give the crude oily product. The crude product was analyzed with mass spectroscopy (FAB): *m/z* 129 $[M + H]^+$, 101, 73; HRMS $[M + H]^+$ calcd for $C_7H_{13}O_2$, 129.0916, found 129.0917.

## ACKNOWLEDGMENT

This work was supported by the National Science Council (NSC 91-2113-M390-001), Taiwan, R.O.C. The authors also thank Prof. Shiuh-Tzung Liu at National Taiwan University for helpful comments and Prof. Ding-Tzai Li (NUK) for obtaining the HRMS.

Received August 12, 2003.

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