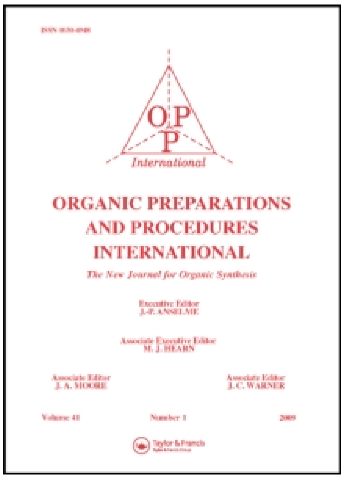

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

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To cite this Article Shan, W. G. , Shi, X. J. and Su, W. K.(2004) 'VILSMEIER-HAACK SYNTHESIS OF AROMATIC ALDEHYDES USING *bis*-(TRICHLOROMETHYL) CARBONATE AND DIMETHYLFORMAMIDE', Organic Preparations and Procedures International, 36: 4, 337 — 340

To link to this Article: DOI: 10.1080/00304940409458675

URL: http://dx.doi.org/10.1080/00304940409458675

ORGANIC PREPARATIONS AND PROCEDURES INT., 36 (4), 337-340 (2004)

VILSMEIER-HAACK SYNTHESIS OF AROMATIC ALDEHYDES USING *bis*-(TRICHLOROMETHYL) CARBONATE AND DIMETHYLFORMAMIDE

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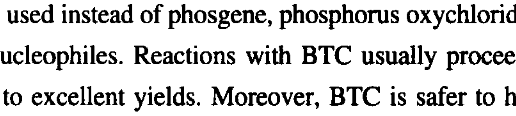
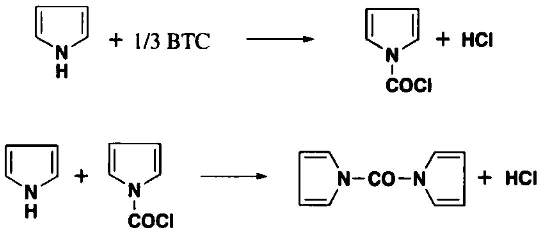
The classical Vilsmeier-Haack reaction is a type of Friedel-Crafts reaction involving electrophilic substitution of suitable carbon nucleophiles with halomethylene-iminium salts.[1] Several substituted aldehydes have been synthesized by the Vilsmeier-Haack reaction.[2-5] The traditional reagents involve a combination of phosphorus oxychloride and *N*-methylformanilide (MFA) or di-methylformamide (DMF). In recent years, the use of dimethylformamide and phosgene as a formylating reagent has found many applications in the preparation of aromatic aldehydes.[6] This paper extends the scope and versatility of the Vilsmeier-Haack reaction through the use of *bis*-(trichloro-methyl) carbonate (BTC) instead of phosphorus oxychloride and phosgene.



$$\underset{\mathbf{1}}{\mathrm{ArH}} \xrightarrow[\mathrm{ClCOCOCCl_3}]{(\mathrm{CH_3})_2\mathrm{NCHO}} \xrightarrow[\mathrm{H_2O}]{\mathrm{NaOH}} \underset{\mathbf{2}}{\mathrm{ArCHO}}$$

a) Ar = p-$(CH_3)_2NC_6H_4$; b) Ar = 2-CH_3O-1-$C_{10}H_6$; c) Ar = 2-C_4H_3S; d) Ar = 5-Br-2-C_4H_2S;
e) Ar = 2-C_4H_3O; f) Ar = 2-C_4H_4N; g) Ar = N-CH_3-2-C_4H_3N

BTC is a useful auxiliary to prepare intermediates for the synthesis of several organic compounds.[7] It may be used instead of phosgene, phosphorus oxychloride and thionyl chloride in reactions with many nucleophiles. Reactions with BTC usually proceed under mild conditions and often afford good to excellent yields. Moreover, BTC is safer to handle and convenient to store and transport because it is a stable solid.



Our experiments show that the formylation of various electron-rich aromatic and heteroaromatic substrates is conveniently carried out by using BTC and DMF as the reagent in carbon tetrachloride. In this system, the formylation of *N*,*N*-dimethyl-aniline, 2-methoxynaphthalene, thiophene, 2-bromothiophene, furan, pyrrole, *N*-methylpyrrole proceeded under mild conditions to give the corresponding aldehydes in good yields (*Table 1*). In comparison to reported methods for the synthesis of aldehydes using other Vilsmeier-Haack reagents, the major advantages of our procedure are its simplicity, the low cost, and the environmentally compatible reagents employed. Although theoretically, 1/3 mole of BTC and one mole of DMF should be sufficient to react with one mole of substrate, it was found that it was necessary to use a 5% excess of the reagent for the total conversion of substrates to aldehydes except for 2-bromothiophene.

Table 1 Preparation of Aldehydes using BTC and DMF in CCl_4[a]

Cmpd	Yield[b] (%)	mp (°C)	*lit.* (°C)	IR(C=O) (cm^{-1})	^1H NMR (δ)	MS(EI) m/z(%)
2a	90	72.8-73.2	74[8]	1605	9.740 (1H, s, CHO), 7.726 (2H, d, *J* = 8.8, ArH), 6.689 (2H, d, *J* = 9.2, ArH), 3.086 (6H, s, CH_3)	----
2b	84	83.1-83.7	84[2]	1665	10.905 (1H, s, CHO), 9.276 (1H, d, *J* = 8.4, ArH), 8.064 (1H, d, *J* = 9.2, ArH), 7.774 (1H, d, *J* = 7.6, ArH), 7.608 (1H, m, ArH), 7.406 (1H, m, ArH), 7.298 (1H, d, *J* = 9.2, ArH), 4.064 (3H, s, OCH_3)	----
2c	87	oil	oil[3]	1674	9.958 (1H, s, CHO), 8.154 (1H, m, ArH), 8.047 (1H, m, ArH), 7.339 (1H, m, ArH)	----
2d	61	oil	oil[3]	1668	9.787 (1H, s, CHO), 7.527 (1H, d, *J* = 4.0, ArH), 7.197 (1H, d, *J* = 4.0, ArH)	192(60) 191(100) 190(58) 189(91)
2e	89	oil	oil[4]	1674	9.670 (1H, s, CHO), 7.731 (1H, t, ArH), 7.299 (1H, d, *J* = 4.0, ArH), 6.631 (1H, m, ArH)	----
2f	82	44-46	44-45[5]	1653	9.720 (1H, s, NH), 9.533 (1H, s, CHO), 7.141 (1H, m, ArH), 6.991 (1H, m, ArH), 6.354 (1H, m, ArH)	----
2g	91	oil	oil[5]	1663	9.528 (1H, s, CHO), 6.899 (1H, m, ArH), 6.882 (1H, m, ArH), 6.193 (1H, m, ArH), 3.939 (3H, s, NCH_3)	----

a) Substrate (2 mmol), DMF (2.1 mmol), BTC (0.7 mmol) and CCl_4 (7 mL) were used. b) Yields based on substrates.

King and Nord[3] had reported that replacement of the bromine atom occurs when 2-bromothiophene reacts with *N*-methylformanilide and phosphorus oxychloride, to yield mainly 5-chloro-2-thiophenecarboxaldehyde. However, in our experiment it was found that replacement of the bromine atom did not take place when 2-bromothiophene reacted with BTC and DMF, to yield only 5-bromo-2-thenaldehyde (**2d**), along with unconverted 2-bromothiophene, even when a 5% excess of the reagent was employed. A possible reason is that the electron-withdrawing effect of the bromine atom of 2-bromothiophene deactivates the ring thus leading to a decreased yield. The structure of 5-bromo-2-thenaldehyde was confirmed by MS, ^{1}H NMR and IR.

As shown in *Table 1*, the yield of pyrrole-2-carboxaldehyde (**2f**) is lower than the 89%[5] obtained using phosphorus oxychloride and DMF as reagent because pyrrole reacts with BTC as shown below.[7]

Our experiments show that the reaction temperature is very important. While the formylation of aromatic amines and naphthyl ether could be carried out under reflux, the reaction of heteroaromatic compounds had to be performed at 40-55°C, otherwise the reaction mixture became black and difficult to process.

In summary, formylation of various electron-rich aromatic and heteroaromatic substrates using DMF and in carbon tetrachloride BTC (instead of phosphorus oxychloride or phosgene), is a viable process which avoids the formation of phosphorous salts and thus will be advantageous in industrial applications from the standpoint of safety and environmental acceptability

EXPERIMENTAL SECTION

Melting points were obtained with a capillary melting point apparatus and were uncorrected. Infrared spectra were recorded on a Thermo Nicolet Avatar 370 spectrophotometer, H^1 NMR spectra (CDCl$_3$ or DMSO-d$_6$) on a Varian Mercur plus-400 spectrometer using TMS as internal standard and mass spectra on a Saturn-2000 MS spectrometer. Organic solvents were obtained from commercial sources. Preparative TCL separations were carried out with silica gel GF-245 coated glass plates. BTC is sold as triphosgene by Aldrich and is listed as a lachrymator.

General Procedure.- In a flask fitted with a thermometer, dropping funnel, condenser, and stirrer was placed pyrrole (2 mmol) and DMF (2.1 mmol). The flask was immersed in an ice-bath, the stirrer was started, and BTC (0.7 mmol) dissolved in carbon tetrachloride (7 mL), was added over a period of fifteen minutes. The mixture was allowed to stir for 15-30 minutes after addition. The ice bath was removed and the mixture was heated to 40-50°C for 2 hr., then cooled and poured into ice water. The solution was made basic with sodium hydroxide. The layers were separated. The aqueous phase was extracted three times with a total of about 30 mL of ether. (If the starting material was furan, the aqueous phase must be saturated with potassium carbonate prior to use because of the solubility of furfural in water.) The ethereal and carbon tetrachloride solutions were combined and dried over sodium sulfate and the solvents were removed under reduced pressure. The residue obtained was subjected to chromatographic purification on TLC silica gel to give pyrrole-2-carboxaldehyde in 82% yield.

Acknowledgement.- We are grateful to the Natural Science Foundation of China (No. 2027602) and the Natural Science Foundation of Zhejiang Province (No. 2001062 and No. 2002095) for financial help.

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(Received May 24, 2004; in final form July 1, 2004)