[CONTRIBUTION NO. 19 FROM THE EXPLORATORY RESEARCH LABORATORY, DOW CHEMICAL OF CANADA, LTD.]

Formylation with Formyl Fluoride: A New Aldehyde Synthesis and Formylation Method[1]

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RECEIVED AUGUST 13, 1959

Using formyl fluoride as acylating agent a new Friedel–Crafts-type aldehyde synthesis and formylation method was developed for the preparation of C-, O-, S- and N-formyl derivatives.

The Friedel–Crafts ketone synthesis using acyl halides or anhydrides as acylation agents is of general use in organic chemistry.[2] Similarly O-, S- and N-acylations can be carried out easily and with excellent yields.

Although a considerable number of aldehyde syntheses and formylation methods are known,[3] no simple method equivalent to the Friedel–Crafts ketone synthesis and acylations with acyl halides or anhydrides has been available, presumably because halides and anhydrides of formic acid are considerably less stable and much less known than those of higher homologous acids.

The only known stable halide of formic acid is the fluoride. Formyl fluoride was first prepared by *Nyesmejanov and Kahn, in 1934,*[4] *in 16% yield* by the interaction of anhydrous formic acid, potassium fluoride and benzoyl chloride. Masentshev[5] prepared it with 36% yield from benzoyl fluoride and formic acid. We have reported its preparation in 35% yield[6] using KHF_2 as the fluorinating agent in the reaction of formic acid and benzoyl chloride.

Although Krauskopf and Rolefson[7a] have claimed the preparation of formyl chloride by the high temperature photochlorination of formaldehyde, this result has never been verified.[7b]

Formic anhydride is generally unknown, although at low temperature it forms intermediately from formyl fluoride and metal formates.[8] Mixed anhydrides of formic acid with higher homologous acids such as acetic formic anhydride are known and quite stable.[9] Acetic formic anhydride is a suitable formylating agent to produce N-formyl derivatives of the corresponding amines.[10] In our investigations we have found, however, that in attempted Friedel–Crafts acylations with acetic formic anhydride only acetylated derivatives are formed, accompanied by carbon monoxide evolution

$$C_6H_6 + CH_3COOOCH \xrightarrow{AlCl_3} C_6H_5COCH_3 + CO + H_2O$$

We have carried out a systematic investigation of the formylation of organic compounds with the stable formyl fluoride. Formyl fluoride was prepared on laboratory scale either with our previously described[6] method or by a new method starting with acetic formic anhydride. If acetic formic anhydride was allowed to react with anhydrous hydrogen fluoride a mixture of formyl fluoride, acetyl fluoride and the corresponding acids is obtained

$$2\ \begin{matrix} CH_3{-}CO \\ \diagdown \\ \quad O \\ \diagup \\ HCO \end{matrix} + 2HF \longrightarrow HCOF + CH_3COF + HCOOH + CH_3COOH$$

Formyl fluoride is easily separated from the reaction mixture.

ADDED AT PROOF.—A 61% over-all yield of formyl fluoride was obtained with only minor amounts of acetyl fluoride formed in the reaction, when acetic formic anhydride was treated with anhydrous hydrogen fluoride at atmospheric pressure and 0°, the formed formyl fluoride being continuously removed during the reaction.

C-Formylation.—Using formyl fluoride as the acylating agent, we have briefly reported[7b,11] the preparation of aromatic aldehydes. Formyl fluoride forms at low temperatures a complex with boron trifluoride, similar to other acylium tetrafluoroborates and this complex was used as the formylating agent in electrophilic aromatic formylations. We have further investigated[12] the reaction mechanism of the interaction of the formylium tetrafluoroborate complex with alkylbenzenes, by isolating ternary σ-complex type intermediates.

We have found now that it is not necessary to prepare the intermediate formyl fluoride–boron trifluoride complex at low temperatures in order to effect aromatic formylation. It is possible to achieve a successful aromatic formylation according to the general Friedel–Crafts acylation reaction by dissolving formyl fluoride in the aromatic and introducing boron trifluoride as a catalyst

$$ArH + FCHO \xrightarrow{BF_3} ArCHO + HF$$

or by passing a formyl fluoride–boron trifluoride mixture through the aromatic hydrocarbons. Similarly boron trichloride or boron tribromide are effective catalysts. In these cases it is advantageous to add the boron halide first to the aromatic hydrocarbon and then introduce formyl fluoride in

(1) Presented at the 135th National Meeting of the American Chemical Society, April 10, 1959, Boston, Mass.

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(3) Houben-Weyl "Methoden der organischen Chemie," Ed. E. Muller, Vol. VII/1 by O. Bayer, Aldehyde, Thieme Verlag, Stuttgart, 1954, pp. 15–412.

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(5) A. I. Masentshev, *J. Gen. Chem. U.S.S.R.*, **16**, 203 (1946).

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TABLE I

Mercaptan (thiophenol)	Thiolformate	B.p., °C.	$n^{25}D$	Mol. wt.	Yield, %	Sulfur, % Calcd.	Sulfur, % Found
Ethyl	Ethyl	94–95[b]	1.4587	90.17	57	35.56	35.57
n-Propyl	*n*-Propyl	125[c]	1.4639	104.17	74	30.77	30.94
n-Butyl[a]	*n*-Butyl	146–148	1.4635	118.2	70	27.08	27.42
Isoamyl[a]	Isoamyl	161–162	1.4604	132.22	78	24.21	24.51
n-Octyl[a]	*n*-Octyl	96–98[d]	1.4651	174.3	72	18.47	18.68
Thiophenol[a]	Phenyl	70–72[e]	1.5820	138.18	58	23.38	23.56

[a] New compounds. Post[13] gave the values [b] 103–106° and [c] 108.5°. [d] 10 mm. [e] 15 mm.

the homogeneous solution. A number of aromatic aldehydes including benzaldehyde, tolualdehyde, tri- and tetramethylbenzaldehyde and naphthaldehyde were prepared with this new aldehyde synthesis in yields from 56 to 78%. Attempted use of aluminum halide catalysts resulted in the decomposition of formyl fluoride. However, a considerable number of other Friedel–Crafts catalysts could be used. Anhydrous silver tetrafluoroborate, cuprous tetrafluoroborate, mercuric tetrafluoroborate, calcium tetrafluoroborate and the corresponding hexafluoroantimonates, hexafluorophosphates and hexafluoroarsenates were successfully applied as cation-forming agent in the formylation reaction.

O-Formylation. (a) Alcohols and Phenols.—Formyl fluoride was found to interact with alcohols and phenols in the presence of an acid-binding agent (such as triethylamine) to form the corresponding formates.

$$ROH + FCHO \longrightarrow ROOCH + HF$$

Alcohols, as methanol, ethanol, 1-propanol, 1-butanol, *sec*-butyl alcohol, *n*-amyl alcohol, isoamyl alcohol and 1-octanol were formylated to the known formates in yields from 73 to 92%, benzyl alcohol with 69% yield and phenol with 75% yield.

(b) **Carboxylic Acid Salts.**—Formyl fluoride was found to react with salts of carboxylic acids to form the corresponding mixed acid-formanhydrides

$$CH_3COONa + FCHO \longrightarrow CH_3COOOCH + NaF$$

Although the same mixed anhydrides are obtainable from metal formates and acyl chlorides, formyl fluoride offers the unique possibility of investigating the possible formation of formic anhydride[8] at low temperatures.

S-Formylation.—Mercaptans and thiophenols react as do their oxygen analogs with formyl fluoride to give the corresponding thiol formates.

$$RSH + FCHO \longrightarrow RSOCH + HF$$

Table I contains the data on the thiol formates prepared.

Thiol formates are little known. Only two members of the group were described by Post[13] as impure by-products in the preparation of thioacetals.

The infrared spectra of the alkyl thiol formates obtained show a strong band at 1681 cm.$^{-1}$ due to the C=O stretching vibration and a strong band at 755–763 cm.$^{-1}$ due to the C—S stretching. Phenyl thiolformate has the C=O stretching frequency at 1698 cm.$^{-1}$ and strong C—S stretching frequencies at 780 and 730 cm.$^{-1}$.

N-Formylation.—As we have reported previously[14] primary and secondary amines react with formyl fluoride to give the corresponding N-alkyl formamides. This work has now been extended and the corresponding N-alkyl formamides were prepared from methyl-, dimethyl-, isopropyl-, dipropyl-, isobutyl-, diisobutyl-, di-*n*-butyl-, octyl-, alkyl-, benzyl-, cyclohexyl-, β-phenylethyl-amine and morpholine in yields from 79 to 93%.

$$2R,R'NH + HCOF \longrightarrow R,R'NCHO + R,R'NH\cdot HF$$

The N-formylation of primary and secondary amines therefore seems to be of general use and can be carried out with good yields.

Tertiary amines, such as triethylamine and pyridine do not react with formyl fluoride in the expected way to form the corresponding formylium salts, but with elimination of carbon monoxide and the formation of the hydrofluorides.

$$N(CH_3)_3 + HCOF \longrightarrow N(CH_3)_3\cdot HF + CO$$
$$C_6H_5N + HCOF \longrightarrow C_6H_5N\cdot HF + CO$$

Experimental

Formyl Fluoride. (a) Preparation from Formic Acid.—To 46 g. (1 mole) of anhydrous formic acid was added 60 g. (0.77 mole) of dry potassium hydrogen fluoride. No warming of the reaction mixture or gas evolution was observed. Then 116 ml. (141 g., 1 mole) of benzoyl chloride was dropped into the stirred mixture and it was slowly heated on a water-bath. During the heating formyl fluoride distilled. Some benzoyl chloride which co-distilled was collected in a condenser cooled with ice–salt, and formyl fluoride not condensing here was collected in a trap cooled with Dry Ice–acetone. It was redistilled in a low temperature column; yield 17 g. (35.4%) of formyl fluoride, b.p. −29°; infrared spectrum in the gas phase shows C=O stretching frequencies at 1835, 1802 and 1739 cm.$^{-1}$, C–F stretching frequencies at 1087, 1075 and 1031 cm.$^{-1}$, C–H stretchings at 2985 and 2941 cm.$^{-1}$. The spectrum is thus identical to that described.[15]

(b) Preparation from Acetic Formic Anhydride.—Acetic formic anhydride (176 g., 2.0 moles) was placed in a small (500 ml.) stainless steel pressure vessel, cooled to Dry Ice temperature and then 40 g. (2.0 moles) of anhydrous hydrogen fluoride was added. The vessel was closed and allowed to warm up slowly to room temperature and shaken for an hour. The outlet valve of the vessel was then connected to a low temperature distillation column and the volatile products were distilled. Formyl fluoride (32 g., 67% of the theoretical yield) boiling at −29° and 92 g. (68%) of acetyl fluoride boiling at +20° were collected.

ADDED AT PROOF.—Carrying out the reaction at atmospheric pressure 88 g. (1.0 mole) acetic formic anhydride (prepared from anhydrous formic acid and ketene) was placed in a fused silica flask connected to a descending condenser provided with a Dry-Ice cooled trap; 20 g. (1.0 mole) anhydrous HF was added at −78° and the temperature of the mixture was then allowed to rise slowly to 0°. It was kept at this temperature for 8 hours. Formyl fluoride as it formed distilled over continuously and was collected in the Dry Ice trap. It was redistilled in a low temperature column, b. p. −29°; yield obtained was 29 g. (0.61 mole) of

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(14) G. Olah and S. Kuhn, *Chem. Ber.*, **89**, 2211 (1956).

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formyl fluoride (61% of the theoretical over-all yield). Only a minor amount of acetyl fluoride was detected.

Aromatic Aldehydes.—(a) Formyl fluoride (24 g., 0.5 mole) was dissolved in 1.0 mole of the corresponding alkylbenzene (toluene, xylene, mesitylene, isodurene) at −30–70° (depending on the freezing point of the hydrocarbon). Into this cold solution boron trifluoride was introduced to saturation (0.5 mole). Generally a deeply colored complex lower layer is formed. The mixture was then allowed slowly to warm up to room temperature. The complex decomposed with strong boron trifluoride evolution. The reaction mixture was washed acid-free with water, dried over calcium chloride and fractionated.

(b) One-half mole of the corresponding aromatic hydrocarbon was dissolved in 150 ml. of CS_2. While the temperature of the reaction mixture was maintained at 0 to 10° a slow stream of formyl fluoride and boron trifluoride (in the ratio of 1:1) was passed through with stirring. After 3 hours when a weight increase corresponding to the reaction of 0.5 mole of formyl fluoride was observed (in the form of the boron fluoride complex) the interaction was stopped, the reaction mixture was stirred for another half-hour, then washed acid-free with cold water, dried over calcium chloride and fractionated. The following aldehydes were prepared: benzaldehyde (56% yield), tolualdehyde (*p*–*o*-isomer mixture, 75%), dimethylbenzaldehyde (mixture, 78%), 2,4,6-trimethylbenzaldehyde (70%), 2,3,4,6-tetramethylbenzaldehyde (72%), naphthaldehyde (α-with about 20% β, 67%).

Alkyl (Aryl) Formates.—One-half mole of the corresponding alcohol (phenol) and 0.5 mole of tri-ethylamine were dissolved in 150 ml. of dry ether. Into the stirred solution was introduced 24 g. (0.5 mole) of formyl fluoride. The temperature of the reaction mixture was kept around 0°. After the addition of the formyl fluoride was completed the stirring was continued for an additional half-hour. The precipitated amine hydrofluoride was filtered off. The ethereal solution was fractionated. The following formates were prepared: methyl (89% yield), ethyl (92%), *n*-propyl (81%), *n*-butyl (80%), *sec*-butyl (84%), *n*-amyl (78%), isoamyl (79%), *n*-octyl (73%), benzyl (69%) and phenyl (75%).

Alkyl (Aryl) Thiolformates—One-half mole of the corresponding mercaptans (thiophenol) and 0.5 mole of triethylamine was dissolved in 200 ml. of dry ether. Formyl fluoride (24 g., 0.5 mole) was introduced into the stirred solution while maintaining the temperature with ice cooling at 0 to 5°. After the addition of the formyl fluoride was completed the stirring was continued for an hour. The precipitated triethylamine hydrofluoride was filtered off and the ethereal solution was fractionated. Date on the thiolformates obtained are summarized in Table I.

Formamides. (a) **Excess Amine as Acid-binding Agent.**—One mole of the corresponding primary or secondary amine was dissolved in 200 ml. of dry ether and treated with 24 g. (0.5 mole) of formyl fluoride while maintaining the temperature about 0°. After the addition of the formyl fluoride was completed the stirring was continued for an additional half-hour. The precipitated amine hydrofluoride was filtered off and the ethereal solution fractionated. (In the case of N-benzyl formamide the ether was distilled off and the solid residue recrystallized from alcohol.) The following N-alkyl formamides were obtained: N-methyl (89% yield), N,N-dimethyl (92%), N-isopropyl (87%), N,N-dipropyl (90%), N-isobutyl (85%), N,N-di-isobutyl (93%), N,N-di-*n*-butyl (86%), N-octyl (88%), N-allyl (79%), N-morpholine (90%), N-benzyl (87%), N-cyclohexyl (83%), N-β-phenylethyl (85%).

(b) **Triethylamine as Acid-binding Agent.**—One-half mole of the corresponding primary or secondary amine and 50.5 g. (0.5 mole) of triethylamine were dissolved in 200 ml. of dry ether and treated with stirring with 24 g. (0.5 mole) of formyl fluoride while maintaining the temperature about 0°. After the addition of the formyl fluoride was completed the stirring was continued for a half-hour. The precipitated amine hydrofluoride was filtered off and the ethereal solution fractionated.

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[CONTRIBUTION FROM THE APPLIED CHEMISTRY DEPARTMENT OF THE INDIAN INSTITUTE OF TECHNOLOGY]

Ease of Cyclization to the β-Lactam Ring[1]

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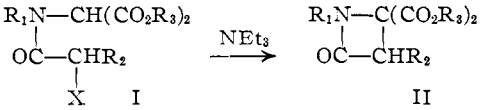
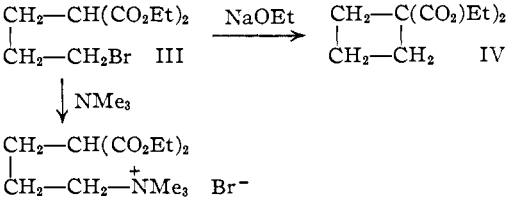
RECEIVED JUNE 24, 1959

The cyclization of ω-haloacylaminomalonic esters in presence of bases has been studied. Four- and five-membered lactams are formed with ease when triethylamine at room temperature is used, but six- and seven-membered lactams are not obtained under these conditions. Attempts to cyclize the N-chloroacetyl derivatives from benzylaniline, phenylglycine ester and α-anilinophenylacetic ester were unsuccessful. Several 3-substituted azetidin-2-ones were prepared by the cyclization of appropriate malonic ester derivatives. Substituents included chloro, bromo and phthalimidomethyl groups.

The method of Sheehan and Bose[3,4] for the synthesis of β-lactams involving the cyclization of an α-haloacetamidomalonic ester I in the presence of such a weak base as triethylamine at room temperature, is reminiscent of Perkin's[5] synthesis of a cyclobutane derivative IV from trimethylene bromide and diethyl malonate. Walborsky[6] has shown that the cyclization of diethyl ω-bromopropylmalonate (III) takes place in presence of such a strong base as sodium alkoxide. When trimethylamine is used as the base, only the quaternary salt from III is formed. The yield of the cyclization product IV, even in the presence of a strong base, is far from quantitative.





The cyclization of I involves the intramolecular alkylation of an amidomalonic ester instead of an alkylmalonic ester as in Perkin's synthesis. Extensive work has been done on the intermolecular alkylation of acetamidomalonic ester and similar

(1) Presented at the 135th Meeting of the American Chemical Society, Boston, Mass., April, 1959. Abstracted from the Ph.D. dissertation of B. N. Ghosh-Mazumdar submitted to the Indian Institute of Technology in 1957.

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