THE CHEMISTRY OF FORMIC ACID AND ITS SIMPLE DERIVATIVES

HARRY W. GIBSON

Chemicals and Plastics Division, Union Carbide Corporation, Tarrytown, New York 10591

Received January 27, 1969

Contents

I. Introduction

Although formic acid and its salts, simple esters, and amides are among the earliest known organic chemicals, no major review of their chemistry has appeared in the technical literature. This is in contrast to the closely related formaldehyde, which has been extensively reviewed.

This article is an attempt to review the literature on formic acid and its simple salts, esters, and amides through 1966. *Chemical Abstracts* was searched under the following headings: formic acid, formates, and formamide. Many more recent references are included, but no attempt was made to exhaustively search the literature after December 1966.

This review is not an in-depth compilation of all the examples of each reaction (an almost insurmountable task). Rather, it is meant to convey the scope (breadth) of reactivity of these compounds and to stimulate interest in some of their unique properties. Thus, only references of primary interest are included.

II. Formic Acid and Its Salts

$HCOOH$ **1**

$HCOO^-$ **2**

A. PHYSICAL PROPERTIES

Formic acid is a colorless liquid which freezes at 8.4° and boils at 101°. The dielectric constant is 58. It has a sharp pungent odor and is miscible in all proportions with water. Formic acid tends to form azeotropes and a variety of these are known.[1] Among the more interesting are those containing tertiary ammonium formates[2-6] which, as shall be seen, have some interesting properties.

Formic acid exhibits severe toxicity as both an acute (short duration) local and acute systemic hazard.[7] It shows slight chronic (long duration) systemic toxicity and moderate chronic local toxicity.[7] Thus, exposure to skin, ingestion, and inhalation should be avoided.

B. CHEMICAL PROPERTIES

1. Structure

The aldehyde-like reducing properties of formic acid (see section II.B.4) encouraged some early chemists to postulate that formic acid is abnormal in structure.[8-10] More modern techniques have shown this not to be the case,[11,12] except that the ether C–O bond is abnormally short, indicating much double-bond character.[13] This undoubtedly contributes to its relatively high acidity.

---

(1) "Azeotropic Data," Advances in Chemistry Series, American Chemical Society, Washington, D. C., 1952, p 23.

(2) E. J. Poziomek and M. D. Pankau, *J. Chem. Eng. Data*, **8**, 627 (1963).

(3) M. Sekiya and K. Ito, *Chem. Pharm. Bull.* (Tokyo), **12**, 677 (1964).

(4) M. Sekiya, K. Ito, A. Hara, and J. Suzuki, *ibid.*, **15**, 802 (1967).

(5) M. Sekiya, Y. Harada, and K. Tanaka, *ibid.*, **15**, 833 (1967).

(6) Farbenfab. Bayer A.-G., Netherlands Patent 6,503,120 (1965); *Chem. Abstr.*, **64**, 6501 (1966).

(7) N. I. Sax, "Dangerous Properties of Industrial Materials," 2nd ed, Reinhold Publishing Corp., New York, N. Y., 1965.

(8) M. Prud'homme, *J. Chim. Phys.*, **16**, 438 (1918).

(9) R. M. Halasyam, *Current Sci.*, **4**, 812 (1936); *Chem. Abstr.*, 30, 5557 (1936).

(10) T. L. Davis and W. P. Green, Jr., *J. Amer. Chem. Soc.*, **62**, 1274 (1940).

(11) R. M. Halasyam, *J. Indian Chem. Soc.*, **12**, 813 (1935); *Chem. Abstr.*, 30, 4149 (1936).

(12) P. B. Sarkar and B. C. Ray, *Nature*, 137, 495 (1936).

(13) R. G. Lerner, J. P. Friend, and H. P. Dailey, *J. Chem. Phys.*, **23**, 210 (1955).

2. Reactions as an Acid

Formic acid is the strongest of the unsubstituted alkanoic monoacids. It has a pK_a of 3.77 as compared with 4.77 for acetic acid. Its relatively high acidity is due to the lack of alkyl groups and their attendant electron release by an inductive effect. This electron release causes destabilization of the carboxylate anions resulting from ionization of the higher monocarboxylic acids.

a. Esterification

The high acidity of formic acid makes use of a mineral acid catalyst unnecessary for esterification of many alcohols (**3**).

$$\mathbf{1} + \underset{\mathbf{3}}{ROH} \longrightarrow \underset{\mathbf{4}}{HCOOR}$$

For example, complete esterification of a series of primary, secondary, and tertiary alcohols at 15° has been reported.[14,15] The rate of esterification in neat formic acid was found to be 15,000–20,000 times that in neat acetic acid.[14]

Formic acid reacts at room temperature with mercaptans (**5**) to yield trithioorthoformates (**6**).[16]

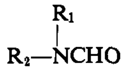
$$\mathbf{1} + \underset{\mathbf{5}}{RSH} \longrightarrow \underset{\mathbf{6}}{HC(SR)_3}$$

Formic acid will also undergo transesterification reactions such as that used to prepare anhydrous acrylic acid (**7**),[17] essentially a hydrolysis without water.

$$\mathbf{1} + CH_2{=}CHCOOCH_3 \longrightarrow \underset{\mathbf{7}}{CH_2{=}CHCOOH} + \mathbf{4}\ (R = CH_3)$$

b. Amidation and Related Reactions

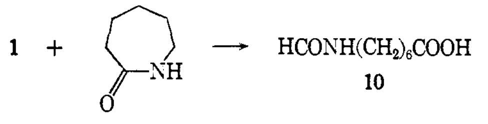
Because of the acidity of formic acid, formylation of most amines occurs readily to yield the expected derivative **8**. For example, in this way N-methylformanilide (**8**, $R_1 = CH_3$; $R_2 = C_6H_5$) is prepared in 93–97% yield.[18]



$$R_2\text{—}\overset{\displaystyle R_1}{\overset{|}{N}}CHO$$

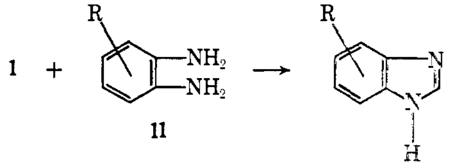
8

Transamidation also occurs with formic acid. ε-Caprolactam (**9**) and formic acid yield 7-formylaminocaproic acid (**10**).[19]



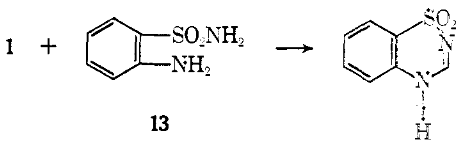
9 **10**

Reaction of diamines with formic acid leads to the formation of imide derivatives. These transformations are of use in syntheses of heterocyclic compounds. 1,2-Diaminobenzenes (**11**) react to form benzimidazoles (**12**) in excellent yields by refluxing the two components;[20,21] the intermediate amide is dehydrated by the excess formic acid normally employed (see section II.B.2.h).



11 **12**

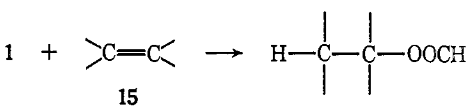
Similarly, the reaction of *o*-sulfonamidoaniline (**13**) with formic acid affords a synthetic pathway to 1,1-dioxobenzothiadiazine (**14**) *via* the intermediate formanilide.[22]



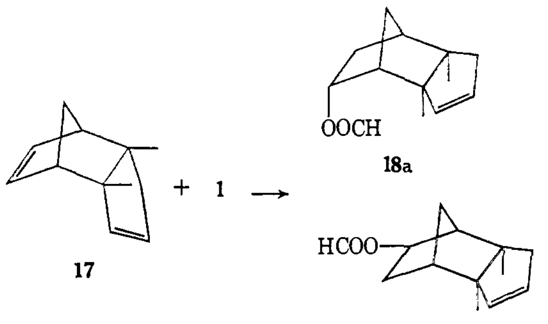
13 **14**

c. Addition to Olefins

Formic acid will undergo Markovnikov addition to olefins (**15**) to yield formate esters (**16**) with greater ease than its homologs. For example, the uncatalyzed addition of 99–100% formic acid to oleic acid is nearly instantaneous, while acetic acid undergoes negligible addition.[23] Excellent yields are usually obtained in the absence of acidic catalyst. Indeed the uncatalyzed addition of formic acid has been used as a quantitative method for determination of dicyclopentadiene (**17**).[24] The structure of the resultant monoformate is known to be *exo* as a result of an "*endo-exo* rearrangement,"[25] but it is not known whether isomer **18a** or **18b** is produced. It would seem that detailed nmr analysis could resolve this question.



$$\mathbf{1} + \underset{\mathbf{15}}{>C{=}C<} \longrightarrow \underset{\mathbf{16}}{H\text{—}\overset{|}{\underset{|}{C}}\text{—}\overset{|}{\underset{|}{C}}\text{—}OOCH}$$



17 **18a** **18b**

---

[14] A. Kailan and N. Friedmann, *Monatsh.*, **62**, 284 (1933).

[15] A. Kailan and F. Adler, *ibid.*, **63**, 155 (1933).

[16] J. Houben, *Chem. Ber.*, 45, 2942 (1912).

[17] C. E. Rehberg, "Organic Syntheses, Coll. Vol., III, John Wiley and Sons, Inc., New York, N. Y., 1955, p 33.

[18] L. F. Fieser and J. E. Jones, ref 17, p 590.

[19] T. Koch and N. Beninnga, U. S. Patent 2,562,797 (1951); *Chem. Abstr.*, **45**, 10674 (1951).

[20] E. C. Wagner and W. H. Millett, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p 65.

[21] N. G. Brink and K. Folkers, U. S. Patent 2,522,854 (1950); *Chem. Abstr.*, **45**, 2510 (1951).

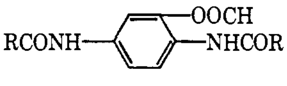
[22] J. Indehev and A. Bruylants, *Bull. Soc. Chim. Fr.*, **74**, 136, 150 (1965).

[23] H. B. Knight, R. E. Koos, and D. Swern, *J. Amer. Chem. Soc.*, **75**, 6212 (1953).

[24] F. Bergmann and H. Japhe, *Anal. Chem.*, **20**, 146 (1948).

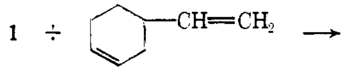
[25] F. Bergmann and H. Japhe, *J. Amer. Chem. Soc.*, **69**, 1826 (1947).

p-Quinonediimides also readily undergo addition of formic acid (among others) to yield **18c**.[26]

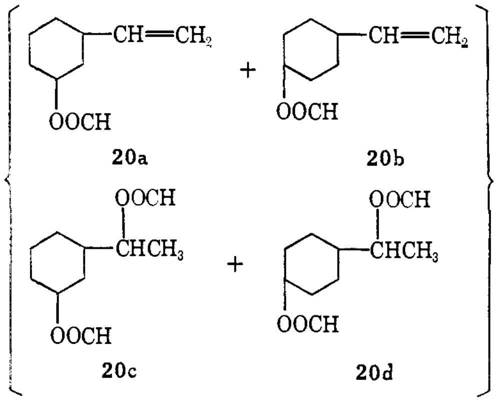


18c

When two or more double bonds are present in a molecule, addition occurs in a way that involves the most stable carbonium ion intermediate. 4-Vinylcyclohexene (**19**) when treated with formic acid yields 61% of the two possible ring addition products **20a** and **20b** and 27% of the two possible diformates **20c** and **20d** and none of the monoformate expected from addition to the side chain.[27]



19



20a 20b

20c 20d

Acetylene reacts with formic acid in the vapor phase to yield vinyl formate (**21**).[28] Although this reaction proceeds

$$1 + HC{\equiv}CH \longrightarrow H_2C{=}CHOOCH$$

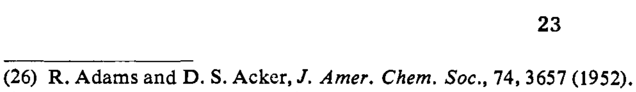
21

readily, another report states that at reflux formic acid does not add to a series of propargyl compounds or 1,4-butynediol.[29]

Formic acid will also undergo addition to olefins in the presence of sulfuric acid or hydrogen fluoride to give rise to acids (section II.B.3b).

d. Cyclization of Aldazines

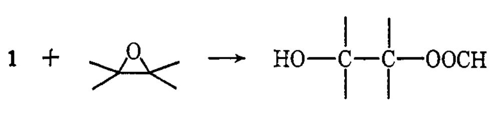
Anhydrous formic acid cyclizes aldazines **22** to N-formylpyrazolines (**23**, R′ = CHO) in good yields.[30] These are readily hydrolyzed to pyrazolines (**23**, R′ = H). The mechanism of the formation of **23** has not been examined, but would appear to include a protonation, hydride shift, and finally a cyclization followed by loss of a proton.



22 23

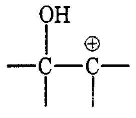
e. Reaction with Epoxides

The reaction of epoxides and formic acid is generally not a synthetically useful reaction (see, however, section II.B.2.k). Though reaction is rapid the expected glycol monoformates (**24**) are accompanied by rearranged materials, *i.e.*, ketones, ethers, and unsaturated compounds.[31] The weaker acids such



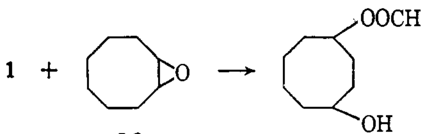
24

as propionic and butyric give good yields of the glycol monoesters, though reaction is slow. With strong acids the first step is protonation and SN1 ring opening, followed by reaction with the carboxylate ion.[32] With formic acid this is true and carbonium ion **25** leads to the formation of by-products. With the less acidic higher molecular weight acids, ring opening may be less SN1 in character so that little free carbonium ion is formed.



25

In the reaction of cyclooctene oxide (**26**) and formic acid, 1,4-cyclooctanediol monoformate (**26a**) is formed by a transannular rearrangement of the intermediate carbonium ion.[33]



26 26a

f. Reagent in the Beckmann Rearrangement

Formic acid is a useful reagent for effecting the Beckmann rearrangement of aromatic ketoximes to amides in yields of 80–95% generally. Cyclohexanone oxime is the only aliphatic ketoxime tested, and it yielded 42% of ε-caprolactam (**9**) under the conditions employed.[34–36]

g. The Rupe (Meyer–Schuster) Rearrangement

In 1926 it was reported that tertiary ethynylcarbinols **27** upon treatment with formic acid are isomerized to unsaturated compounds.[37] Unsaturated aldehydes were then believed to be the products.[38–40] However, subsequent work has shown that

---

(26) R. Adams and D. S. Acker, *J. Amer. Chem. Soc.*, 74, 3657 (1952).

(27) R. C. Kuder, U. S. Patent 2,764,610 (1954); *Chem. Abstr.*, **51**, 4420 (1957).

(28) E. N. Rostovskii and I. A. Arbuzova, *Met. i. Khim. Prom. Kazakhstana, Nauchn.-Tekhn. Sb.*, 71 (1961); *Chem. Abstr.*, 58, 5489 (1963).

(29) J. Jadot and S. Mullers, *Bull. Soc. Roy. Sci. Liege*, 29, 203 (1960).

(30) A. N. Kost and I. I. Grandberg, *Zh. Obshch. Khim.*, **26**, 2319 (1956); *Chem. Abstr.*, **51**, 5054 (1957).

(31) W. J. Hickenbottom, "Reactions of Organic Compounds," Longmans Green and Co., New York, N. Y., 1957, p 171.

(32) W. J. Hickenbottom and D. R. Hogg, *J. Chem. Soc.*, 4200 (1954).

(33) A. C. Cope, S. W. Fenton, and C. F. Spencer, *J. Amer. Chem. Soc.*, 74, 5884 (1952).

(34) T. van Es, *J. Chem. Soc.*, 3881 (1965).

(35) J. Meisenheimer, W. Theilacker, and O. Beiszwenger, *Ann. Chem.*, **495**, 249 (1932).

(36) K. von Auwers and O. Jordan, *Chem. Ber.*, 58, 26 (1925).

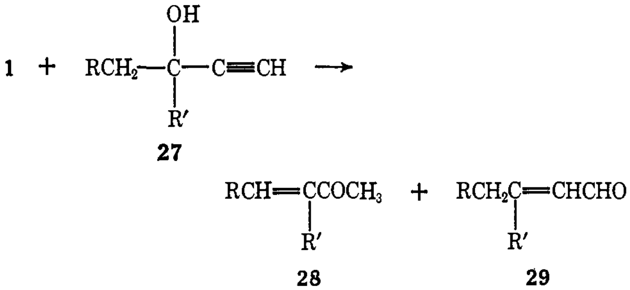
(37) H. Rupe and E. Kambli, *Helv. Chim. Acta*, **9**, 672 (1926).

(38) H. Rupe, W. Messner, and E. Kambli, *ibid.*, **11**, 449 (1928).

(39) H. Rupe and L. Giesler, *ibid.*, **11**, 656 (1928).

(40) H. Rupe, A. Wirz, and P. Lotter, *ibid.*, 11. 965 (1928).

the main products are unsaturated ketones **28**,[41] although the unsaturated aldehydes **29** are formed in small amounts[42] and, on occasion, in appreciable quantities.[43,44] The mechanism of the reaction involves dehydration (see section II.B.2.h) to a vinylacetylene, followed by hydration of the triple bond.[45]

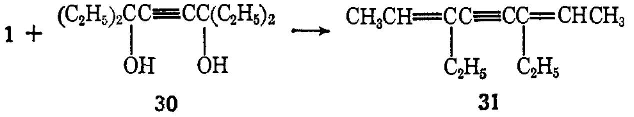


$$1 + RCH_2{-}\underset{R'}{\overset{OH}{C}}{-}C{\equiv}CH \longrightarrow \underset{28}{RCH{=}\underset{R'}{C}COCH_3} + \underset{29}{RCH_2\underset{R'}{C}{=}CHCHO}$$

Secondary acetylenic carbinols **27** (R′ = H) lose acetylene, yielding an aldehyde which undergoes an acid-catalyzed aldol reaction.[46]

h. Dehydration

Formic acid brings about dehydration in many instances. For example, refluxing it with **30** yields **31**.[47] Examples of the cyclodehydration of formamides by formic acid were presented in section II.B.2.b.



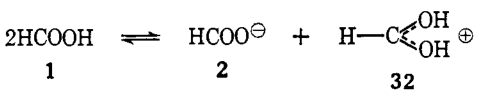
$$1 + \underset{30}{(C_2H_5)_2\underset{OH}{C}C{\equiv}C\underset{OH}{C}(C_2H_5)_2} \longrightarrow \underset{31}{CH_3CH{=}\underset{C_2H_5}{C}C{\equiv}C\underset{C_2H_5}{C}{=}CHCH_3}$$

The pinacol rearrangement of 1,2-diols is a dehydration which involves a 1,2-alkyl shift in an intermediate carbonium ion; formic acid brings about this transformation with little or no side reaction.[48]

In section II.B.5 are discussed solvolysis reactions which are closely related to these dehydration reactions in that a hydroxyl moiety is removed as water, leaving a carbonium ion.

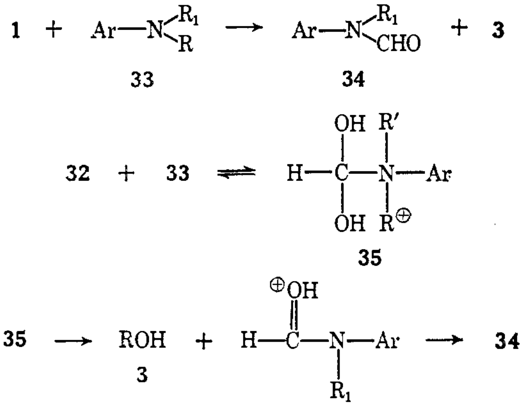
i. Autoprotolysis

Formic acid has a large autoprotolysis constant, that is, the equilibrium constant for formation of **32**[49] (see section II.B.3.b for further discussion of **32**).

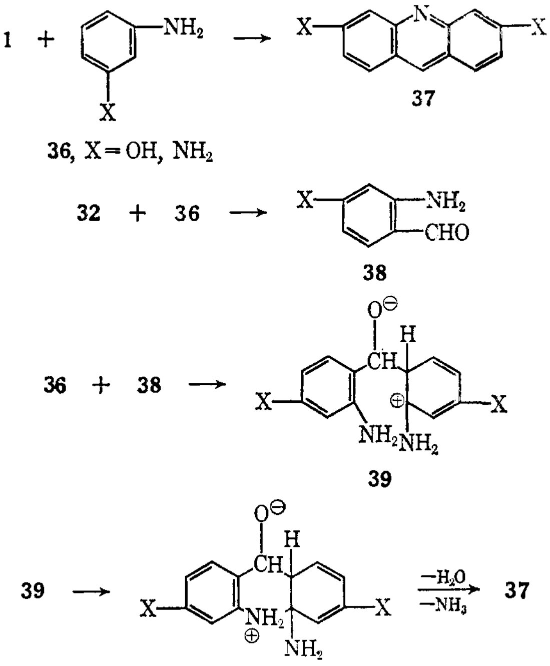


$$\underset{1}{2HCOOH} \rightleftharpoons \underset{2}{HCOO^{\ominus}} + \underset{32}{H{-}C(OH)_2^{\oplus}}$$

The protonated species **32** apparently takes part in several reactions. Treatment of aromatic tertiary amines with azeotropes of amines and formic acid causes dealkylation (generally less than 50% yield) as illustrated with general structure **33**. Reaction of **32** and **33**, leading to **35**, is postulated. This then dissociates to the alcohol **3** and the protonated form of **34**. This mechanistic proposal is consonant with the effect of substituents on the aromatic ring and the basicities of the tertiary amines.[50]



Species **32** may be envisioned as a participant in the synthesis of acridines (**37**) from formic acid and *m*-hydroxy- or *m*-aminoanilines (**36**) in the presence of hydrochloric acid.[51,51a]



The reaction probably proceeds *via* **38** formed from **32** and **36** by loss of water. Reaction of **38** and **36** could then lead to **39**, which could yield the products by the sequence shown. Sometimes the products are formed by loss of one of the X substituents of intermediate **39** *via* a similar pathway. Additional deamination and/or dehydroxylation sometimes occurs as evidenced by isolation of monosubstituted acridines.[51]

j. Reaction with Grignard Reagents

Reaction of Grignard reagents (**40**) with anhydrous formic acid gives rise to low yields of aldehydes,[52,53] presumably by

---

(41) G. K. Fischer and K. Loewenberg, *Ann. Chem.*, 475, 183 (1929).

(42) J. D. Chanley, *J. Amer. Chem. Soc.*, 70, 244 (1948).

(43) T. Takeshima, K. Wakamatsu, and A. Furukashi, *Bull. Chem. Soc. Japan*, 31, 640 (1958); *Chem. Abstr.*, 53, 10067 (1959).

(44) T. Takeshima, K. Nagoka, M. Yokoyama, and S. Morita, *ibid.*, 32, 547 (1959); *Chem. Abstr.*, 54, 7539 (1960).

(45) G. F. Hennion, R. B. Davis, and D. E. Maloney, *J. Amer. Chem. Soc.*, 71, 2813 (1949).

(46) J. Jadot and N. Doyen, *Bull. Soc. Roy. Sci. Liege*, 24, 2 (1955).

(47) V. N. Krestinskii and N. Summ, *Zh. Obshch. Khim.*, 7, 440 (1937); *Chem. Abstr.*, 31, 4268 (1937).

(48) J. F. Lane and L. Spialter, *J. Amer. Chem. Soc.*, 73, 4411 (1951).

(49) R. P. Bell, "Acids and Bases," Methuen and Co., Ltd., London, 1952, pp 33 ff.

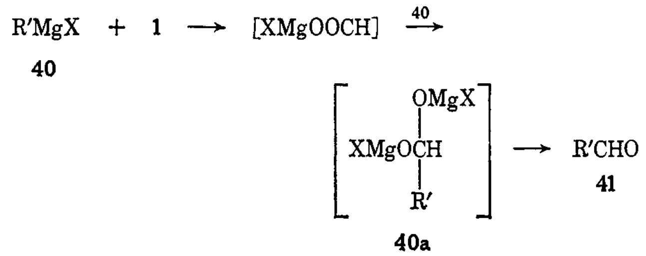
(50) M. Sekiya, M. Tomic, and N. J. Leonard, *J. Org. Chem.*, 33, 318 (1968).

(51) A. Albert, *J. Chem. Soc.*, 1225 (1948).

(51a) A. Albert, *ibid.*, 244 (1947).

(52) J. Houben, *Chem. Ztg.*, 29, 667 (1905).

(53) N. D. Zelinsky, *ibid.*, 28, 303 (1904).



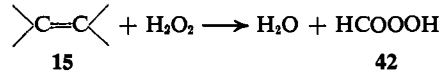
$$R'MgX + \mathbf{1} \longrightarrow [XMgOOCH] \xrightarrow{\mathbf{40}} \left[\begin{matrix} OMgX \\ XMgOCH \\ R' \end{matrix}\right] \longrightarrow R'CHO$$

40 **40a** **41**

way of intermediate **40a**. Reaction of copper formate also gives low yields of **41**.[52]

k. Reaction with Hydrogen Peroxide

Performic acid (**42**) results from treatment of formic acid with hydrogen peroxide, *via* displacement of water from protonated



$$>C=C< + H_2O_2 \longrightarrow H_2O + HCOOOH$$

15 **42**

hydrogen peroxide by formate ion. The reaction is acid catalyzed. Performic acid has been obtained in 90% purity,[53a] but owing to its instability is usually not isolated. Generated *in situ* it has been used for the preparation of glycol formates (**24**) from olefins (**15**).[54,55]

$$\mathbf{15} + \mathbf{42} \longrightarrow \mathbf{24}$$

The reaction involves formation of an intermediate epoxide which is attacked by formic acid (section II.B.2.e). Over-all *trans* addition of the peracid occurs.

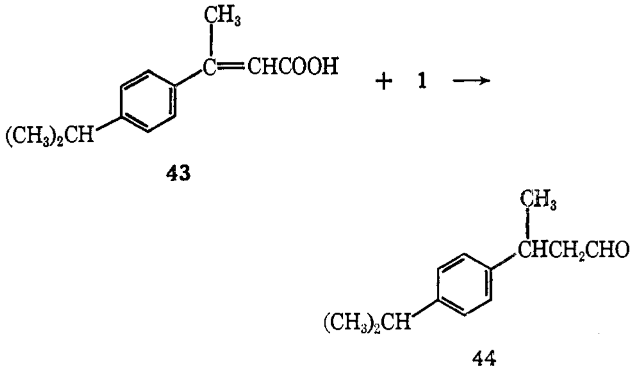
3. Decomposition Reactions

a. Formation of Carbon Dioxide and Hydrogen

Formic acid decomposes to carbon dioxide and hydrogen over a copper oxide–chromium oxide catalyst at 160–180°[56] or a platinum, iridium, rubidium, palladium, or osmium surface in the presence of oxygen at 150°.[57] A wide variety of other metallic compounds bring about this decomposition.[58]

The reduction of olefinic bonds and of acids to aldehydes by formic acid at high temperature and pressure probably involves this reaction. 3-(*p*-Isopropylphenyl)-3-methylpropionaldehyde (**44**) has been prepared from the corresponding cinnamic acid **43** in this way.[59]

Salicylaldehyde (among others) has reportedly been prepared in 92% yield in this way from salicylic acid over titanium dioxide.[60] The validity of this particular piece of work has been challenged, however.[61] In view of this, the general applicability of this procedure for the reduction of acids to aldehydes is questionable.



The reduction of nitro compounds to amines by carbon monoxide and water in an alkaline medium[62] may involve formation of formate ion followed by evolution of carbon dioxide and hydrogen, the active reducing species. Aromatic ketones are reduced to hydrocarbons and aldehydes and aliphatic ketones to alcohols in this way.[63–65]

Electrolysis of formic acid gives rise to carbon dioxide and hydrogen without peroxide formation according to a recent report.[66] However, an earlier publication describes formyl peroxide as an intermediate in the formation of carbon dioxide and formaldehyde.[67] In view of the more modern treatment, this appears unlikely.

Hydrogen and carbon dioxide would seem to arise *via* a bimolecular reaction of formate ions[68] and also by way of a bimolecular reaction of formate ion and formic acid.[69]

Raney nickel catalyzes the decomposition of formic acid and formate ion at ordinary temperatures. Thus, by carrying out a reduction with Raney nickel in formic acid the hydrogen on the catalyst is constantly replenished. Using this technique olefins, ketones,[70] and aldehydes[71] have been reduced. Raney nickel has also been used to catalyze the reduction of imines[72,73] (see section II.B.4.a).

b. Formation of Carbon Monoxide and Water

Generation of high-purity (99.9%) carbon monoxide from formic acid can be achieved by the use of sulfuric acid.[74] Other mineral acids can also be used.[75–78]

(53a) J. d'Ans and A. Kneip, *Chem. Ber.*, **48**, 1136 (1915).

(54) D. Swern, J. T. Scanlan, and G. B. Dickel, "Organic Syntheses," Coll. Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1963, p 317.

(55) A. Roebuck and H. Adkins, ref 17, p 217.

(56) N. V. deBataafsche Petroleum Maatschappij., British Patent 844,598 (1960); *Chem. Abstr.*, **55**, 9283 (1961).

(57) H. G. P. van der Voort, U. S. Patent 2,913,492 (1959); *Chem. Abstr.*, **54**, 14127 (1960).

(58) P. Sabatier and A. Mailhe, *C. R. Acad. Sci., Paris, Ser. C.*, **152**, 1212 (1911).

(59) S. Shinya, *Nippon Nogei-Kagaku Kai Shi*, **29**, 94 (1955); *Chem. Abstr.*, **53**, 1228 (1950).

(60) R. R. Davies and H. H. Hodgson, *J. Chem. Soc.*, 84 (1943).

(61) A. J. Barduhn and K. A. Kobe, *ibid.*, 1651 (1954).

(62) E. A. Swakon and E. Field, U. S. Patent, 3,293,295 (1966); *Chem. Abstr.*, **66**, 65272 (1967).

(63) A. Mailhe. *J. Usines Gaz.*, **49**, 147 (1925); *Chem. Abstr.*, **19**, 2334 (1925).

(64) A. Maihle and F. De Godon, *Bull. Soc. Chim. Fr.*, **21**, 61 (1917).

(65) M. Heintzeler, German Patent 933,337 (1955); *Chem. Abstr.*, **52**, 16298 (1958).

(66) S. D. Ross, M. Finkelstein, and R. L. Petersen, *J. Org. Chem.*, **31**, 128 (1966).

(67) E. Bauer, *Helv. Chim. Acta*, **11**, 372 (1928).

(68) V. Komarov, E. A. Chernikova, and G. V. Komarov, *Zh. Fiz. Khim.*, **36**, 540 (1962); *Chem. Abstr.*, **57**, 1605 (1962).

(69) K. Horota, T. Otaki, and S. Asai, *Z. Physik. Chem.*, **21**, 438 (1959).

(70) K. Ashida, *Mem. Inst. Sci. Ind. Res., Osaka Univ.*, **8**, 193 (1951); *Chem. Abstr.*, **45**, 7043 (1951).

(71) R. Staskun and O. G. Backberg, *J. Chem. Soc.*, 5880 (1964).

(72) A. N. Kost, A. P. Terent'ev, and G. A. Schvekhgeimer, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 150 (1951); *Chem. Abstr.*, **45**, 10194 (1951).

(73) A. N. Kost and N. I. Stupnikova, *Zh. Obshch. Khim.*, **26**, 2485 (1956); *Chem. Abstr.*, **52**, 4964 (1958).

(74) A. L. Mossman, U. S. Patent 2,996,359 (1961); *Chem. Abstr.*, **56**, 3124 (1962).

(75) A. G. Taylor and W. A. Caldwell, U. S. Patent 2,645,661 (1953); *Chem. Abstr.*, **47**, 9347 (1953).

(76) C. F. Binder, U. S. Patent 116,142 (1871).

(77) A. A. Fesquet, U. S. Patent 44,053 (1864).

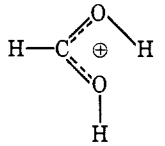
(78) J. V. L. Longstaff and K. Singer, *J. Chem. Soc.*, 2604, 2610 (1954).

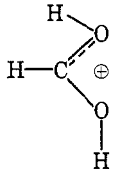
The reaction mechanism is believed to involve protonation of the formic acid, giving **32**, followed by loss of water. This

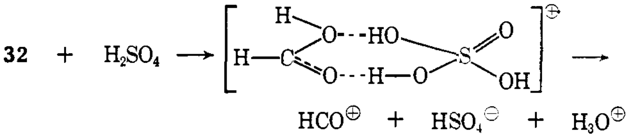
$$\mathbf{1} + H^{\oplus} \longrightarrow \mathbf{32} \longrightarrow H_2O + HCO^{\oplus} \longrightarrow CO + H^{\oplus}$$

generates an incipient highly unstable formylium ion (protonated carbon monoxide) which readily gives up a proton.[79]

A recent pmr study of formic acid in the systems hydrofluoric acid–boron trifluoride and hydrofluoric acid–antimony pentachloride at −67° revealed the presence of **32** in two distinct planar conformations **32a** and **32b** in a 77:23 ratio, respectively.[80] No protonated carbon monoxide could be detected. The surprising lack of dehydration in these strong acids was alleged to their inability to hydrogen bond with **32** as is possible with sulfuric acid, as illustrated.


32a

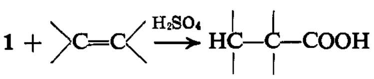

32b



In the system sulfur dioxide–fluorosulfonic acid–antimony pentafluoride at −60°, **32a** and **32b** are present in nearly equal amounts. Acetic acid by contrast exists in a cisoid form analogous to **32a** to the extent of about 97%, presumably due to the steric effect of the methyl group.[81]

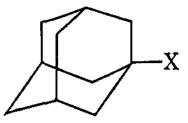
Chlorosulfonic acid ($ClSO_3H$) causes the decomposition of formic acid to carbon monoxide and hydrogen chloride.[82] This is a convenient method of preparing the equimolar mixture of these gases required in the Gatterman-Koch reaction for preparation of aldehydes.

Reaction of formic acid and an olefin (**15**) in the presence of sulfuric or hydrofluoric acid results in formation of acid **45**. This is known as the Koch reaction and has been thoroughly reviewed.[83] It involves formation of incipient carbon monoxide. Since a carbonium ion is formed, rearrangements often occur, resulting in mixtures of carboxylic acids.



$$\mathbf{1} + \underset{\mathbf{15}}{>C{=}C<} \xrightarrow{H_2SO_4} \underset{\mathbf{45}}{HC{-}C{-}COOH}$$

Compounds which are precursors of olefins can also be carboxylated in this way. Among this class are alcohols[84] and alkyl halides.[85] Examples of these reactions are the production of adamantanecarboxylic acid (**46**, X = COOH) from either the alcohol **46** (X = OH) or the bromide **46** (X = Br) in 96% yield.[86]


46

In the presence of sulfuric acid and an alcohol or olefin, hydrocarbons are carboxylated by formic acid. The reaction involves removal of a hydride ion from the hydrocarbon to form a carbonium ion. The product results from the most stable carbonium ion. Incipient carbon monoxide is also involved here. Rearrangements are common. In this way adamantane (**46**, X = H) yields 80% of adamantanecarboxylic acid (**46**, X = COOH).[87,88] This reaction has been recently discussed.[89]

Carbon monoxide and water result from contact of formic acid and metallic compounds at elevated temperatures.[58,90] It has been suggested that carbon monoxide and water result from a secondary reaction of carbon dioxide and hydrogen once formed (see section II.B.3.a) and that at high temperatures the secondary reaction is very fast, giving the impression of a direct reaction second order in formic acid.[91] This suggestion would also readily account for the cooccurrence of both sets of products in many instances of thermal decomposition,[58,92,93] but it seems likely that the mechanism is similar to that in photolysis.

The photolysis of formic acid, which also gives rise to both sets of decomposition products, does not generate free radicals. No methyl radicals or hydrogen atoms are formed. The reactions are viewed as single step molecular rearrangements.[94,95]

c. Formation of Formaldehyde

A third type of decomposition which occurs concomitantly is the autoreduction of formates or formic acid in the presence of metals. Formaldehyde is formed in low yields (25% or less).[93,96–98] The formaldehyde may result from direct autoreduction or from a secondary reaction of the hydrogen and carbon monoxide produced. Methanol is produced by further reduction of formaldehyde.[58] In addition methane has been reported.[93,97] Acetone, furfural derivatives, and pyruvic acid are also formed, but purportedly result from oxalic and glyoxalic acid precursors[97] (see section II.B.6).

4. Formic Acid as a Reducing Agent

From the above discussion of decomposition reactions of formic acid one might have predicted that formic acid could serve as a reducing agent, in view of its propensity to lose

---

(79) G. A. Ropp, *J. Amer. Chem. Soc.*, **80**, 6691 (1958).

(80) H. Hogeveen, A. F. Bickel, C. W. Hilbers, E. L. Mackor, and C. Maclean, *Rec. Trav. Chim. Pays-Bas*, **86**, 687 (1967).

(81) G. A. Olah and A. M. White, *J. Amer. Chem. Soc.*, **89**, 3591 (1967).

(82) L. Bert, *C. R. Acad. Sci., Paris, Ser. C*, **221**, 77 (1945).

(83) G. A. Olah and J. A. Olah in "Friedel Crafts and Related Reactions," Vol. 3, G. A. Olah, Ed., Interscience Publishers, New York, N. Y., 1964, p 1284.

(84) Reference 83, p 1290.

(85) Reference 83, p 1300.

(86) W. Haaf, *Org. Syn.*, **46**, 72 (1966).

(87) H. Stetter, M. Schwarz, and A. Hirschborn, *Chem. Ber.*, **92**, 1629 (1959).

(88) H. Koch and W. Haaf, *Angew. Chem.*, **72**, 628 (1960).

(89) Reference 83, p 1302.

(90) J. S. MacKenzie, U. S. Patent 2,656,379 (1953); *Chem. Abstr.*, **48**, 13714 (1954).

(91) J. A. Muller and E. Peytral, *Bull. Soc. Chim. Fr.*, **29**, 34 (1921).

(92) V. Sihvonen, *Suomen Kemistilehti*, **12B**, 15 (1939); *Chem. Abstr.*, **33**, 6693 (1939).

(93) K. Hofmann and H. Schibsted, *Chem. Ber.*, **51**, 1389 (1918).

(94) M. Burton, *J. Amer. Chem. Soc.*, **58**, 1655 (1936).

(95) P. Kebarle and F. P. Lossing, *Can. J. Chem.*, **37**, 389 (1959).

(96) V. Yakhontov, *Zh. Obshch. Khim.*, **17**, 2054 (1947); *Chem. Abstr.*, **42**, 4888 (1948).

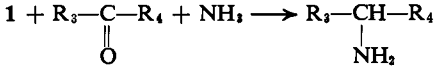
(97) K. Hofmann and K. Schumpelt, *Chem. Ber.*, **49**, 303 (1916).

(98) B. Melis, *Giorn. Chim. Ind. Applicata*, **6**, 327 (1924); *Chem. Abstr.*, **19**, 36 (1925).

both hydrogens and form carbon dioxide. Indeed formic acid *per se* has been used to reduce a wide variety of organic compounds.

a. Reduction of Imines

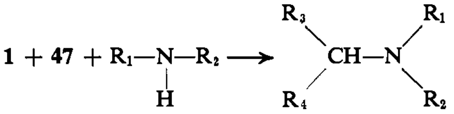
Reduction of imines (Schiff bases) by formic acid has long been known. The Leuckart reaction is probably the best known example of reduction by formic acid. Primary amines (**48**) are prepared from ketones (**47**), ammonia, and formic acid. The reaction was reviewed in 1949.[99] Formamides may be substituted for the formic acid–amine combination (see section V.B.1.d). In fact, some authors have claimed formamide is the active reagent in all these reactions.[100–102] However, since the reaction occurs below the temperature necessary for formamide formation (~150°)[103] and different products have been observed with formamide and ammonium formate,[104] it appears that the ammonia gives rise to an imine, which is reduced by formic acid to the amine (**48**).[105]



$$1 + R_3\text{—}\underset{\underset{\displaystyle O}{\|}}{C}\text{—}R_4 + NH_3 \longrightarrow R_3\text{—}\underset{\underset{\displaystyle NH_2}{|}}{CH}\text{—}R_4$$

47 **48**

The Wallach reaction is an extension of the Leuckart reaction. Reaction of a ketone (**47**) or aldehyde (**47**, R_3 = H), formic acid, and a primary (**49**, R_2 = H) or secondary amine (**49**) produces a secondary (**50**, R_2 = H) or tertiary amine (**50**).

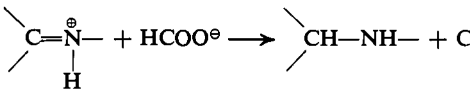


49 **50**

The mechanism again presumably involves reduction of an imine or in the case of the secondary amine an enamine (see section II.B.4.b) by formic acid or formate ion. This reaction has also been discussed as a modification of the Leuckart reaction.[99]

The Eschweiler–Clark methylation of amines with formaldehyde and formic acid[99] is but another example of the Wallach reaction. An N-methylenimmonium ion appears to be reduced by formate ion.[105]

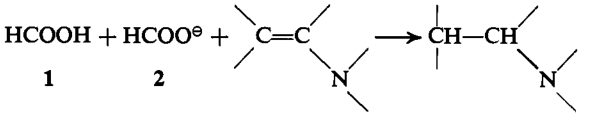
The reduction of imines *per se* by formic acid and formate ion is also known.[4,103,106–109] Hydrazones and azines are also reduced by formic acid and sodium formate to the corresponding hydrazines.[110] Probably as proposed[4,111,112] these reductions occur *via* the iminium ion **51** resulting from protonation. Hydride transfer from formate ion would then yield the observed products, amine and carbon dioxide. One author, however, favors a free-radical pathway.[113]



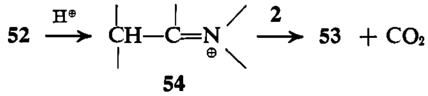
51 **2**

b. Reduction of Enamines

Enamines (**52**) are reduced by formic acid–formate ion to the saturated compounds **53**.[114–117] The course of this reduction has been shown to include hydride transfer to the protonated enamine (**54**) by formate ion.[117] Deuterated formic acid was used for this study.

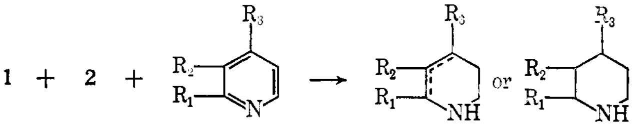


1 **2** **52** **53**



54

This type of enamine reduction also undoubtedly occurs in the reduction of pyridine derivatives (**55**) to the piperidine (**57**) or tetrahydropyridine (**56**) compounds. The reduction of quinolines or isoquinolines (**55**, R_1, R_2 = benzo or R_2, R_3 = benzo, respectively) leads to products of type **56**.[118,119] Piperidines (**57**) result when a benzo group is not attached to the pyridine nucleus.[118,120–122]



55 **56** **57**

An imminium type salt is formed by protonation. This is then reduced as a Schiff base by formate ion to an enamine. Part of the hydride transfer occurs at the 4 position giving rise to two enamine functions in one molecule. Both of these are reduced. The rest of the hydride is transferred to the 2 and 6 positions, yielding a molecule containing a single enamine function. This is reduced but the isolated double bond is not; so a mixture of tetrahydropyridine (**56**) and piperidine (**57**) results. The benzopyridines suffer reduction only to the tetra-

---

(99) M. L. Moore, *Org. Reactions*, **5**, 301 (1949).

(100) V. J. Webers and W. F. Bruce, *J. Amer. Chem. Soc.*, **70**, 1422 (1948).

(101) A. N. Kost and I. I. Grandberg, *Zh. Obshch. Khim.*, **25**, 1432 (1955); *Chem. Abstr.*, **50**, 4800 (1956).

(102) A. F. Rekasheva and G. P. Miklukhin, *ibid.*, **26**, 2407 (1956); *Chem. Abstr.*, **51**, 4978 (1957).

(103) E. R. Alexander and R. B. Wildman, *J. Amer. Chem. Soc.*, **70**, 1187 (1948).

(104) R. K. Barnes and G. H. Warner, private communication, 1965.

(105) P. Le Henaff, *C. R. Acad. Sci., Paris, Ser. C*, **258**, 3690 (1964).

(106) R. Boltzly and O. Kouder, *J. Org. Chem.*, **16**, 173 (1951).

(107) A. Lukasiewicz and Z. Eckstein, *Rocz. Chem.*, **39**, 695 (1965); *Chem. Abstr.*, **64**, 3521, (1966).

(108) Z. Eckstein and A. Lukasiewicz, *Przem. Chem.*, **39**, 367 (1960); *Chem. Abstr.*, **55**, 3501 (1961).

(109) A. Lukasiewicz, *Bull. Acad. Pol. Sci., Ser. Sci. Chim.*, **7**, 789 (1959); *Chem. Abstr.*, **54**, 24679 (1960).

(110) A. N. Kost and I. I. Grandberg, *Zh. Obshch. Khim.*, **25**, 1719 (1955); *Chem. Abstr.*, **50**, 5544 (1956).

(111) C. B. Pollard and D. C. Young, Jr., *J. Org. Chem.*, **16**, 661 (1951).

(112) A. I. Titov and A. N. Boryshnikova, *Zh. Obshch. Khim.*, **23**, 290 (1953); *Chem. Abstr.*, **48**, 2704 (1954).

(113) A. Lukasiewicz, *Tetrahedron*, **19**, 1789 (1963).

(114) P. L. Benneville, U. S. Patent 2,578,787 (1951); *Chem. Abstr.*, **46**, 9518 (1952).

(115) R. Lukes and V. Dedek, *Chem. Listy*, **51**, 2082 (1957).

(116) R. Lukes and O. Cervinka, *ibid.*, **51**, 2142 (1957).

(117) N. J. Leonard and R. R. Sauers, *J. Amer. Chem. Soc.*, **79**, 6210 (1957).

(118) L. G. Yudin, A. N. Kost, Y. A. Berlin, and A. E. Shipov, *Zh. Obshch. Khim.*, **27**, 3021 (1957); *Chem. Abstr.*, **51**, 8142 (1957).

(119) A. N. Kost and L. G. Yudin, *ibid.*, **25**, 1947 (1955); *Chem. Abstr.*, **50**, 8644 (1956).

(120) A. N. Kost. L. G. Yudin, and A. E. Shipov, *Vestn. Mosk. Univ., Ser. Mat., Mekhan. i. Astron., Fiz. i. Khim.*, **11**, 209 (1956); *Chem. Abstr.*, **52**, 9114 (1958).

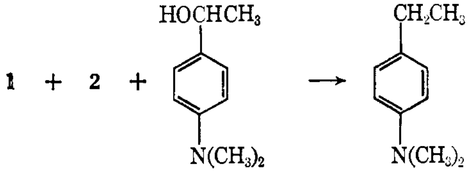
(121) O. Cervinka and O. Kriz, *Collect. Czech. Chem. Commun.*, **30**, 1700 (1965).

(122) O. Cervinka, *Chem. Listy*, **59**, 1058 (1965).

hydro state since further reduction would result in loss of resonance energy. Quaternized pyridines are similarly reduced.[121]

c. Reduction of Benzyl Alcohols and Related Compounds

Reduction of α-(*p*-dimethylaminophenyl)ethanol (**58**) to *p*-dimethylaminophenylethane (**59**) in 6% yield by formic acid and formate ion has been reported.[103] The reduction of triarylcarbinols (**60**, X = OH) has long been known. The corresponding hydrocarbons (**60**, X = H) result in generally quantitative yields.[123–126] It is also possible to reduce derivatives of the triarylcarbinols to the hydrocarbons. Triarylmethyl ethyl ethers (**60**, X = OCH_2CH_3) and triarylcarbinyl chlorides (**60**, X = Cl) have been so reduced.[127]


58 **59**

$$(Ar)_3\text{—C—X}$$
60

All of these reactions proceed *via* formation of stable triarylcarbonium ion formates (**61**). Hydride transfer from formate ion to the carbonium ion forms the hydrocarbon and carbon dioxide.[127–129] Kinetics substantiate that prior ionization is necessary in view of the linear relationship between rate constants and ionization constants for the carbinols.[130] The slope indicates a half-formed C–H bond in the transition state.[130]

$$1 + 60 \longrightarrow \underset{61}{(Ar)_3C^{\oplus}\ {}^{\ominus}OOCH} + H_2O$$

The silicon analogs, the triarylsilanols (**62**, X = OH), are also reduced by formic acid.[131] However, silanes **62** (X = H) do not result. Rather the main products are the arenes (**63**) resulting from reductive cleavage of the aryl–silicon bond. The chloride **62** (X = Cl) appears to be inert, but the silane **62** (X = H) undergoes cleavage to **63**,[131] implying that it may be an intermediate in the reaction.

$$1 + \underset{62}{Ar_3SiX} \longrightarrow \underset{63}{ArH}$$

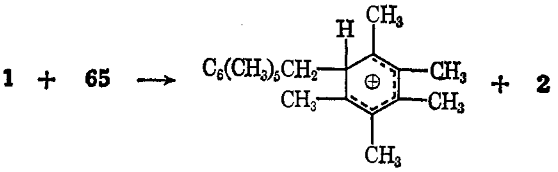
d. Reduction of Diarylmethanes

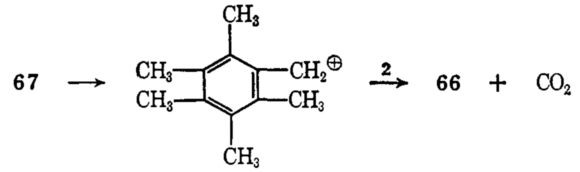
Refluxing pentamethylbenzene (**64**) and formaldehyde in formic acid solution for 1 hr leads to the formation of bis-(pentamethylphenyl)methane (**65**) in good yield. Continued reflux leads to the formation of hexamethylbenzene (**66**) in 80% yield.[132] Attempts to bring about methylation on less heavily benzenes lead only to Novalak and/or Bakelite-type products.[133]

$$HCHO + 1 + \underset{64}{C_6H(CH_3)_5} \longrightarrow \underset{65}{C_6(CH_3)_5CH_2C_6(CH_3)_5}$$

$$1 + 65 \longrightarrow \underset{66}{C_6(CH_3)_6}$$

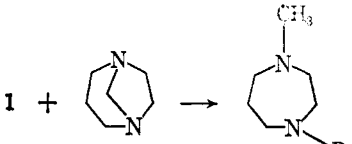
A plausible mechanism might be protonation of the electron-rich diarylmethane to give a structure such as **67**, followed by loss of the pentamethylphenylcarbonium ion, which could be reduced by formate ion to the observed product **66**.

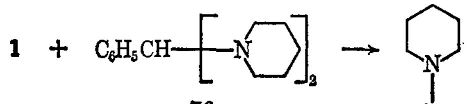

67



e. Reduction of Diaminomethanes, Sulfonylaminomethanes, and Acylaminomethanes

Diaminomethanes suffer reductive cleavage by formic acid to a monoaminomethane and a formamide (*via* a primary or secondary amine). 1,5-Diazabicyclo[3.2.1]octane (**68**) is converted to 1-methyl-4-formylhomopiperazine (**69**, R = CHO), presumably *via* **69** (R = H).[134]


68 **69**


70 **71**

N,N′-Benzylidenebispiperidine (**70**) undergoes a similar reductive cleavage to N-benzylpiperidine (**71**, R = $CH_2C_6H_5$) and N-formylpiperidine (**71**, R = CHO) by formic acid at room temperature.[135]

Acylaminomethyl and sulfonylaminomethyl compounds undergo reductive fission by formic acid–tertiary amine azeotropes to yield unsubstituted amides or sulfonamides and the methyl compounds. For example, N-benzamidomethylpiperidine (**72**) affords 97% of N-methylpiperidine (**71**, R = CH_3) along with benzamide.[3]

---

(123) A. Guyot and A. Kovache, *C. R. Acad. Sci., Paris, Ser. C*, **154**, 21 (1912); **155**, 838 (1913); **156**, 1324 (1913).

(124) A. Kovache, *Ann. Chim.*, **10**, 184 (1918).

(125) H. Kauffmann and P. Pannwitz, *Chem. Ber.*, **45**, 766 (1912).

(126) C. N. Wolf and R. L. Shriner, *J. Org. Chem.*, **15**, 367 (1950).

(127) S. T. Bowden and T. F. Watkins, *J. Chem. Soc.*, 1333 (1940).

(128) R. Stewart, *Can. J. Chem.*, 766 (1957).

(129) R. Grinter and S. F. Mason, *Trans. Faraday Soc.*, **60**, 882 (1964).

(130) R. Grinter and S. F. Mason, *ibid.*, **60**, 889 (1964).

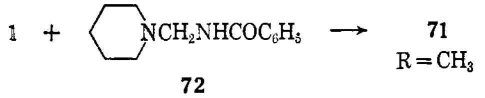
(131) H. Gilman and K. Oita, *J. Amer. Chem. Soc.*, **77**, 3386 (1955).

(132) L. Kriebaum, Abstracts, 153rd National Meeting of the American Chemical Society, Miami, Fla., April 1967, No. O-186.

(133) H. W. Gibson, unpublished results.

(134) G. M. Goodale and F. Popplesdorf, private communication, 1962.

(135) E. Staple and E. C. Wagner, *J. Org. Chem.*, **14**, 559 (1949).

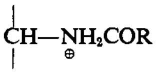


72

Reaction of these azeotropes and N,N′-benzylidenebisamides (73) yields acylbenzylamines (74) and amides 75.[5]

$$1 + 2 + \underset{73}{ArCH(NHCOR)_2} \longrightarrow \underset{74}{ArCH_2NHCOR} + \underset{75}{H_2NCOR}$$

These reactions most likely involve protonation of nitrogen. The protonated species (76) may then be reduced by formate ion by hydride transfer.



$$\overset{|}{\underset{|}{C}}H—\underset{\oplus}{N}H_2COR$$

76

f. Reduction of Inorganic Compounds

Reduction of some inorganic materials (oxidizing agents) by formic acid also occurs. Among the most significant of these are those involving sulfur compounds. The peroxydisulfate ($S_2O_8^{2-}$) reduction to sulfate (SO_4^{2-}) can be catalyzed by silver ion.[136] Sulfur dioxide (SO_2) is reduced at 25° to thiosulfate ion ($S_2O_3^{2-}$) *via* the radical ion $SO_2\cdot^-$ and hydrosulfite ion ($S_2O_4^{2-}$).[137] The formic acid–tertiary amine azeotropes will reduce sulfur dioxide to elemental sulfur in good yield at 100°.[133]

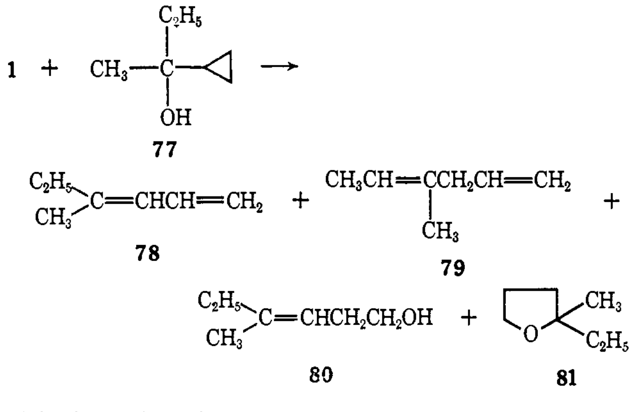
The normal inorganic oxidizing agents (dichromate, permanganate) are, of course, reduced by formic acid. The reduction of lead tetraacetate is the basis of a method for quantitative determination of formic acid.[138,139]

5. Solvolysis Reactions

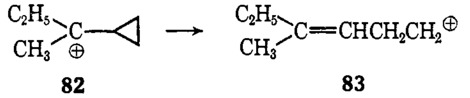
Use of formic acid in solvolysis reactions has produced a massive volume of literature. Formolyses have been intimately involved in the nonclassical carbonium ion dialogue. Solvolysis reactions have been defined as those in which the solvent combines with the substrate.[140] Many of the reactions discussed to this point thus fall into this category.

However, in this section attention will be focused on several reactions not readily classified in the above sections, as well as some comparative characteristics of formic acid noted in solvolytic reactions.

Tertiary cyclopropylcarbinols undergo rearrangement when solvolyzed (see section II.B.2.h on Dehydration). For example, methylethylcyclopropylcarbinol (77) produces olefins 78, 79, and 80 resulting from ring opening, and furan 81, formed by ring opening and a subsequent ring closure.[141] Similar compounds give like results.[142–144]

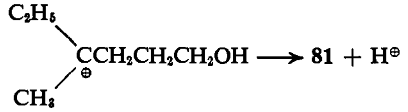


The formation of these compounds can be explained by the intermediacy of carbonium ion 82, which subsequently loses a proton to form the normal dehydration products. Rearrangement of 82 gives 83, which can react with water to form 80 or lose a proton to give 78. Protonation of the double bond in 80



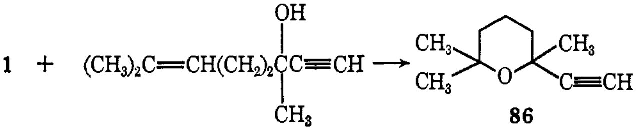
82 83

followed by intramolecular attack of the hydroxyl oxygen of the resultant carbonium ion (84) would give the protonated form of 81.



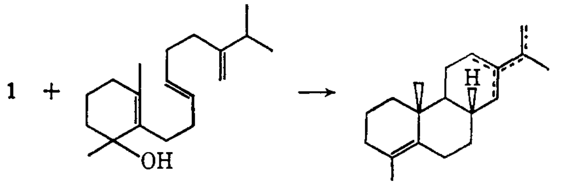
84

A reaction similar to the latter has been reported in the formation of 86 from dehydrolinalool (85) and formic acid.[145]



85 86

One of the most interesting uses of solvolytic reactions in terms of our understanding of stereochemistry of biosynthetic processes is the cyclization of complex polyolefins. An example of this is the conversion of 87 to 88 by treatment with formic acid at room temperature for 11 min.[146] The reaction



87 88

probably proceeds by way of the carbonium ion resulting from protonation of the hydroxyl group and loss of water. This topic is the subject of a short review.[147]

Formolysis reactions have yielded information about the

---

(136) Y. K. Gupta and R. K. Nigam, *J. Indian Chem. Soc.*, **37**, 125 (1960).

(137) M. Goliath and B. O. Lindgren, *Acta Chem. Scand.*, **16**, 570, (1962).

(138) A. S. Perlin, *Anal. Chem.*, **26**, 1053 (1954).

(139) J. E. Ruch and F. E. Critchfield, private communication, 1958.

(140) E. R. Thornton, "Solvolysis Mechanisms." The Ronald Press Co., New York, N. Y., 1964, p 1.

(141) T. A. Favorskaya and N. V. Scherbinskaya, *Zh. Obshch. Khim.*, **23**, 1667 (1953); *Chem. Abstr.*, **48**, 13638 (1954).

(142) T. A. Favorskaya and N. V. Scherbinskaya, *Zh. Obshch. Khim.*, **23**, 1485 (1953); *Chem. Abstr.*, **48**, 11358 (1954).

(143) T. A. Favorskaya, N. V. Scherbinskaya, and S. E. Chernobel'skaya, *Zh. Obshch. Khim.*, **20**, 855 (1950); *Chem. Abstr.*, **44**, 9358 (1950).

(144) T. A. Favorskaya, *Zh. Obshch. Khim.*, **11**, 1246 (1941); *Chem. Abstr.*, **39**, 4047 (1945).

(145) Badische Anilin and Soda Fabrik A.-G., Belgian Patent 681,526 (1966).

(146) W. S. Johnson, N. P. Jensen, and J. Hooz, *J. Amer. Chem. Soc.*, **88**, 3859 (1966).

(147) W. S. Johnson, *Accounts Chem. Res.*, **1**, 1 (1968).

nucleophilicity and ionization power of formic acid. In nucleophilicity, formic acid appears to be less powerful than any of the commonly used solvent systems.[148] However, formic acid is second only to water in ionizing power, *i.e.*, the ability of a solvent to promote ionization of species by an SN1-type process.[149,150] This property depends on solvation qualities to a greater extent than on dielectric constant.[151] The coupling of these two factors is responsible for the higher proportion o by-products observed in formic acid solvolyses (see section II.B.2.e). Detailed discussions of formolytic reactions in general can be found in texts on the subject.[140,152]

6. Free-Radical Reactions

Very few authenticated examples of free-radical reactions of formic acid are known. This is due to the propensity for excited formic acid molecules to undergo single-step molecular rearrangement to decomposition products without the intermediacy of free radicals[95,153] (see section II.B.3.b).

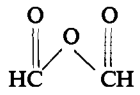
Photolysis of formic acid has been reported to yield oxalic acid,[155] but this has been disproven.[95,156] The formation of oxalic acid in low yield by photolysis of an aqueous formic acid–carbon dioxide solution has been reported, however.[157] Thus, if water is present photolysis could conceivably yield oxalic acid. The photolysis of water yields hydrogen atoms and hydroxy radicals. The former react with hydroxyl ion to form a solvated electron which can transform carbon dioxide to $CO_2\cdot^-$ radical ion. Interaction of formate ion and hydrogen atom or hydroxy radical can also form this radical ion. The reaction of the radical ion with formate ion is a chain reaction which yields oxalate ion.[157]

Metal formates are converted in good yields to oxalates by heating to 360–440°.[158–166] The reaction is possibly a free-radical process occurring on the metal atom.[97]

Reaction of chlorine with formic acid in ultraviolet light gives rise to hydrogen chloride and carbon dioxide,[167] possibly *via* unstable chloroformic acid.[168]

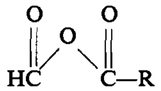
III. Formic Anhydrides and Formyl Halides

The anhydride and halides of formic acid are much less stable than the higher homologs and were unknown until the last 40 years. Formic anhydride (**89**) has never been isolated although it apparently is formed fleetingly at low temperature from formyl fluoride (see below) and metal formates.[169,170] Incipient formic anhydride reportedly also is formed from formic acid by the action of dicyclohexylcarbodiimide[171] or cyanamide.[172]



89

Mixed anhydrides of formic acid (**90**), on the other hand, are easily prepared and are relatively stable. For example, benzoyl chloride and sodium formate (**2**) yield formic benzoic anhydride (**90**, R = C_6H_5).[173] Formic acetic anhydride (**90**, R = CH_3) can be prepared from formic acid and acetic anhydride[174] or ketene.[175]



90

These mixed anhydrides react with alcohols to yield nearly exclusively formates[176] and with amines to form formamides.[177,178] Use of the mixed anhydrides in Friedel–Crafts acylation reactions results in evolution of carbon monoxide (from the formyl group) and formation of the acylated compound from the other portion of the anhydride.[170,179]

The only known formyl halide is the fluoride (**91**, X = F). It was first prepared in 1934 in 16% yield from benzoyl chloride, potassium fluoride, and anhydrous formic acid.[180]

$$HCOX$$

91

It can now be prepared in 61% yield from formic acetic anhydride (**90**, R = CH_3) and hydrofluoric acid.[170] It boils at −29°. Its spectral properties and use as a Friedel–Crafts formylating agent have been summarized.[181]

---

(148) C. G. Swain, R. B. Mosley, and D. F. Brown, *J. Amer. Chem. Soc.*, 77, 3731 (1955).

(149) A. H. Fainberg and S. Winstein, *ibid.*, 79, 1597, 1602, 1608 (1957); 78, 2770 (1956).

(150) S. Winstein, A. H. Fainberg, and E. Grunwald, *ibid.*, **79**, 4146 (1957).

(151) S. G. Smith, A. H. Fainberg, and S. Winstein, *ibid.*, **83**, 618 (1961).

(152) A. Streitwieser, Jr., "Solvolytic Displacement Reactions," McGraw-Hill Book Co., Inc., New York, N. Y., 1962.

(153) M. Burton, *J. Amer. Chem. Soc.*. 58, 1655 (1936).

(154) Deleted in revision.

(155) L. Farkas and O. H. Wansbrough-Jones, *Z. Physik. Chem.*, **B18**, 124 (1932); *Chem. Abstr.*, **26**, 5259 (1932).

(156) K. Pfordte and G. Leuschner, *Ann. Chem.*, **622**, 1 (1959).

(157) N. Getoff, *Photochem. Photobiol.*, **4**, 433 (1965).

(158) W. Wallace, Canadian Patent 213,377 (1921); *Chem. Abstr.*, **16**, 1100 (1922).

(159) W. Wallace, U. S. Patent 1,506,872 (1924); *Chem. Abstr.*, **18**, 3386 (1924).

(160) A. Hempels, British Patent 4897 (1908); *Chem. Abstr.*, **2**, 2348 (1908).

(161) A. Hempels, French Patent, 389,039 (1908): *Chem. Abstr.*, **2**, 2351 (1908).

(162) H. W. Paulus, U. S. Patent, 1,420,213 (1922); *Chem. Abstr.*, **16**, 2868 (1922).

(163) Oldbury Electro Chemical Co., British Patent, 174,126 (1920); *Chem. Abstr.*, **16**, 2335 (1922).

(164) H. W. Paulus, U. S. Patents 1,445,162 and 1,445,163 (1923); *Chem. Abstr.*, 17, 1242 (1923).

(165) S. Keimatsu and B. Ikeda, *J. Pharm. Soc. Japan*, **399**, 499 (1915); *Chem. Abstr.*, **9**, 2232 (1915).

(166) L. Freidlin, *Zh. Prikl. Khim.*, **11**, 975 (1938); *Chem. Abstr.*, **33**, 1661 (1939).

(167) G. A. Ropp, C. E. Melton, and P. S. Rudolph, *J. Chem. Phys.*, 34, 688 (1961).

(168) H. L. West and G. K. Rollefson, *J. Amer. Chem. Soc.*, 58, 2140 (1936).

(169) G. Olah, A. Pavlath, S. J. Kuhn, and G. Varsanyi, "Elektronentheorie der homopolaren Bindung," Akademie Verlag, Berlin, 1955, p 79.

(170) G. Olah and S. J. Kuhn, *J. Amer. Chem. Soc.*, 82, 2380 (1960).

(171) I. Muramatsu, M. Itoi, M. Tsuji, and A. Hagitani, *Bull. Chem. Soc. Japan*, 37, 756 (1964); *Chem. Abstr.*, 61, 8184 (1964).

(172) A. Kretov and A. Momsenko, *Zh. Obshch. Khim.*, 31, 3916 (1961); *Chem. Abstr.*, 57, 12314 (1962).

(173) G. F. Fanta, *J. Org. Chem.*, **29**, 981 (1964).

(174) A. Behal, *C. R. Acad. Sci., Paris, Ser. C*, **128**, 1460 (1899).

(175) C. D. Hurd and A. S. Roe, *J. Amer. Chem. Soc.*, **61**, 3355 (1939).

(176) W. Stevens and A. van Es, *Rec. Trav. Chim. Pays-Bas*, **83**, 1287 (1964).

(177) G. R. Clemo and G. Swan, *J. Chem. Soc.*, 603 (1945).

(178) C. Huffman, *J. Org. Chem.*, **23**, 727 (1958).

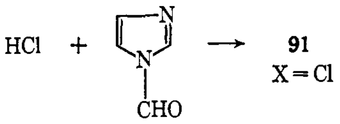
(179) W. Edwards and E. Sibille, *ibid.*, **28**, 674 (1963).

(180) A. N. Nesmejanov and E. Kahn, *Chem. Ber.*, 67, 370 (1934).

(181) G. A. Olah and S. J. Kuhn in ref 83, p 1179.

Formyl fluoride also reacts with alcohols and phenols, forming formates; with amines, forming formamides; with carboxylic acid salts, forming mixed acid formic anhydrides (**90**).[170]

Formyl chloride (**91**, X = Cl) has been generated by low-temperature reaction of N-formylimidazole (**92**) and hydrogen chloride. It has never been isolated but was successfully derivatized.[182]



92

IV. Formate Esters

$HCOOR$
4

A. PHYSICAL PROPERTIES

Formate esters are typical esters in physical properties. They are volatile, flammable, sweet-smelling liquids. They are only slightly soluble in water.

These esters are of moderate acute (short duration) local and systemic toxicity.[7] They are irritating to the skin and mucous membranes.[7] In high concentration they are narcotic.[7]

B. CHEMICAL PROPERTIES

1. Electrophilic Reactions

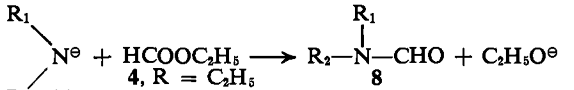
Being esters, formates are electrophilic and undergo many useful electrophilic reactions.

a. Hydrolysis

Formate esters are easily hydrolyzed to the parent alcohol and formic acid. Bicarbonate is sometimes sufficient.[183]

b. Reaction with Amines

Formates can be used for the formylation of amines (**49**). Ethyl formate in particular has seen much use in this connection. The N-formyl derivatives (**8**) are obtained in good yields simply by heating the two components.[184-187] Only a small part of the reaction takes place *via* reaction of the neutral species. Reaction of the amide ion **93** with ethyl formate yields the formamide **8** and ethoxide ion. The reaction is catalyzed by bases and retarded by acids; a high positive neutral salt effect is also consonant with this description.[188] Esters of higher acids do not acylate amines under comparable conditions.[184,185]



$$R_1R_2N^{\ominus} + \underset{\mathbf{4},\ R\,=\,C_2H_5}{HCOOC_2H_5} \longrightarrow \underset{\mathbf{8}}{R_2\text{—}\overset{R_1}{\overset{|}{N}}\text{—}CHO} + C_2H_5O^{\ominus}$$

93

c. Transesterification

Formate esters also undergo transesterification reactions with alcohols. This is an especially useful technique for releasing high-boiling alcohols from their formate esters through use of methanol and for hydrolysis of formates which are sensitive to acid or base. For example, acetol (**3**, R = CH_3COCH_2) has been released from its formate in this way.[189]

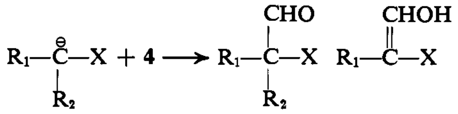
d. Reaction with Alkoxides

Formation of ethers (**95**) in good yields by reaction of alkoxides (**94**) with formate esters at 0° has been reported.[190] The reaction appears formally to be a displacement of formate ion (**2**) by attack of the alkoxide ion on the carbon α to the ether oxygen.

$$\underset{\mathbf{94}}{R'O^{\ominus}} + \mathbf{4} \longrightarrow \underset{\mathbf{95}}{R'OR}$$

e. Reaction with Carbanions

Formate esters react with carbanions (**96**) which are formed from treatment of compounds containing acidic hydrogen with base. Into this class fall esters, ketones, and nitriles. In the reaction an alkoxide ion is displaced from the formate (**4**), and a formylated derivative (**97**) is formed. These products usually exist in the tautomeric hydroxymethylene form (**98**) if one of the substituents (*e.g.*, R_2) is hydrogen.



$$\underset{\mathbf{96}}{R_1\text{—}\overset{\ominus}{\underset{R_2}{C}}\text{—}X} + \mathbf{4} \longrightarrow \underset{\mathbf{97}}{R_1\text{—}\overset{CHO}{\underset{R_2}{C}}\text{—}X} \quad \underset{\mathbf{98}}{R_1\text{—}\overset{CHOH}{\overset{\|}{C}}\text{—}X}$$

X = COR, COOR, CN

The yields and stabilities of the products vary considerably. Unsymmetrical ketones yield mixtures of the two possible isomers. The formylation of ketones has been discussed in perspective with acylation of ketones in general.[191]

The reaction with esters is very similar except that there is no orientation problem. The method has been used as a route to aldehydes by decarboxylating the β-aldehydo acid formed through hydrolysis.[192] It has been used to prepare precursors for heterocycles[193] and steroids.[194] The reaction of nitriles with formates has not been widely used, but appears to be similar to those discussed above.[195]

A closely related reaction is that involving an alkoxide (**94**), acrylonitrile (**99**), and a formate ester (**4**).[196] The product **100** results from reaction of the ester **4** and the carbanion **96** (X = CN; R_1 = $ROCH_2$; R_2 = H) formed by attack of the alkoxide ion (**94**) on the olefin.

---

(182) H. Staab and A. P. Datta, *Angew. Chem.*, **75**, 1203 (1963); ref 83, p 1154.

(183) M. Salmon, H. Estrada, and F. Walls, *Bol. Inst. Quim. Univ. Nacl. Auton. Mex.*, 17, 181 (1965); *Chem. Abstr.*, **64**, 8963 (1966).

(184) M. Sekiya, *J. Pharm. Soc. Japan*, 70, 553 (1950); *Chem. Abstr.*, **45**, 5619 (1951).

(185) J. P. E. Human and J. A. Mills, *J. Chem. Soc.*, 1457 (1948).

(186) C. G. Overgerber and S. L. Shapiro, *J. Amer. Chem. Soc.*, **76**, 93 (1954).

(187) J. Moffatt, M. V. Newton, and G. J. Papenmaier, *J. Org. Chem.*, **27**, 4058 (1962).

(188) W. H. Watanabe and L. P. DeFonso, *J. Amer. Chem. Soc.*, **78**, 4542 (1956).

(189) P. A. Levene and A. Walti, ref 20, p 5.

(190) S. B. S. Gupta and R. Das, *J. Indian Chem. Soc., Ind. News Ed.*, 13, 259 (1950); *Chem. Abstr.*, **46**, 2481 (1952).

(191) C. R. Hauser, *Org. Reactions*, **8**, 59 (1954).

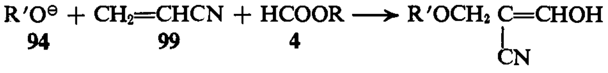
(192) E. Elkik, *Bull. Soc. Chim. Fr.*, 2254 (1964).

(193) E. C. Kornfield and R. G. Jones, *J. Org. Chem.*, **19**, 1671 (1954).

(194) H. L. Holmes and L. W. Trevoy, ref 17, p 300.

(195) F. Eiden and B. S. Nagar, *Arch. Pharm.*, **297**, 367 (1964).

(196) I. A. Rubstov, M. V. Balyakina, E. S. Zhdanovich, and N. A. Preobrazhenskii, *Tr. Vses. Nauchn.-Issled. Vitamin. Inst.*, **4**, 23 (1953); *Chem. Abstr.*, **50**, 4009 (1956).

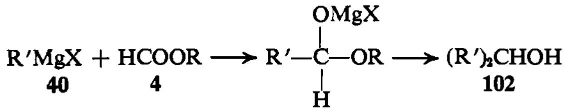


$$\underset{94}{R'O^{\ominus}} + \underset{99}{CH_2{=}CHCN} + \underset{4}{HCOOR} \longrightarrow R'OCH_2\underset{\substack{|\\ CN}}{C}{=}CHOH$$

100

f. Reaction with Grignard Reagents

The reaction of Grignard reagents (**40**) with formates generally leads to the expected secondary alcohols **102**, presumably *via*



$$\underset{40}{R'MgX} + \underset{4}{HCOOR} \longrightarrow R'{-}\overset{\substack{OMgX\\ |}}{\underset{\substack{|\\ H}}{C}}{-}OR \longrightarrow \underset{102}{(R')_2CHOH}$$

101

intermediate **101** with displacement of alkoxide.[197,198] The presence of certain metallic impurities (such as cobaltic chloride) can bring about formation of the hydrocarbon **103**, among other products.[199]

$$\underset{103}{R'CH_2R'}$$

A synthetic route to aldehydes (**41**) by the low-temperature (–70 to 20°) hydrolysis of intermediate **101** formed in excess ester has been developed.[200–205] Aromatic Grignard reagents generally provide about a 50% yield of the aldehydes,[203,205] while yields as high as 90% were reported recently with aliphatic Grignards.[200]

g. Friedel–Crafts Formylation

Reaction of aromatic compounds (**63**) with alkyl formates in the presence of aluminum chloride yields only the alkylated products (**104**) and no aldehydes.[206,207] Hydrolysis of the esters

$$\underset{63}{ArH} + \underset{4}{HCOOR} \xrightarrow[\text{acid}]{\text{Lewis}} \underset{104}{Ar{-}R}$$

to alkyl halides and dichloroaluminum formates is formally proposed.[206]

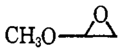
Attempted Fries rearrangement of phenyl formate in the presence of aluminum chloride or boron trifluoride results only in a complex mixture; no *p*-hydroxybenzaldehyde is formed. Apparently decarbonylation and secondary reactions occur.[208]

h. Reaction with Diazomethane

The reaction of formate esters with diazomethane apparently leads to formation of acetates. Formic acid yields methyl acetate (**105**).[209] This probably occurs *via* methyl formate (**4**, R = CH_3) in view of the ease of reaction of acids with diazomethane.

$$\underset{1}{HCOOH} + CH_2N_2 \longrightarrow \underset{4,\ R\ =\ CH_3}{HCOOR} \xrightarrow{CH_2N_2} \underset{105}{CH_3COOCH_3}$$

In the presence of ultraviolet light methyl formate (**4**, R = CH_3) and the carbene from diazomethane yield a mixture of insertion products.[210] Insertion into the C–C bond leads to ethyl formate (**4**, R = C_2H_5). Methoxyethylene oxide (**105a**) and methoxyacetone (**47**, $R_3 = CH_3$; $R_4 = CH_2OCH_3$) result from C–O insertion processes. Other products result from further reaction of these materials.

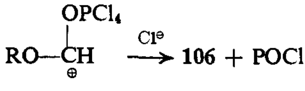


105a

i. Reaction with Phosphorus Pentachloride

Treatment of formate esters with phosphorus pentachloride results in the formation of α,α-dichloromethyl ethers (**106**).[211] In this reaction formate esters behave like aldehydes and ketones. The mechanism is probably similar to that in ketones, which has to date received the most attention. Though the mechanism is far from clear, intermediate **107** seems likely by analogy with mechanistic proposals for the reaction of ketones and phosphorus pentachloride.[211a] Attack of chloride ion and loss of phosphorus oxychloride by rearrangement would then yield **106**.

$$4 + PCl_5 \longrightarrow \underset{106}{ROCHCl_2}$$



$$RO{-}\overset{\substack{OPCl_4\\ |}}{\underset{\oplus}{CH}} \xrightarrow{Cl^{\ominus}} 106 + POCl_3$$

107

The dichloromethyl ethers are useful intermediates for Friedel–Crafts formylation of aromatics[212] and as carbene precursors in the synthesis of alkoxycyclopropanes.[213,214]

2. *Decomposition Reactions*

a. Reaction with Strong Bases

It has long been known that formates in the presence of strong bases such as sodium hydride, alkoxides, and triphenylmethylsodium are decomposed to alkoxides and carbon monoxide.[215,216] Early workers proposed the intermediate formation of the divalent carbon compound **108** by action of alkoxide on formate esters and claimed to have isolated it in one instance.[216–218] This was later shown to be incorrect.[219] Re-

$$\underset{108}{RO{-}C{-}O^{\ominus}\ Na^{\oplus}}$$

---

(197) G. H. Coleman and D. Craig, ref 20, p 179.

(198) W. G. Young and J. D. Roberts, *J. Amer. Chem. Soc.*, 68, 649 (1946).

(199) I. Lapkin and A. I. Golovkova, *Zh. Obshch. Khim.*, 21, 117, (1951); *Chem. Abstr.*, 45, 7081 (1951).

(200) L. I. Zakharkin and L. P. Sorokina, *Zh. Organ. Khim.*, 3, 1758 (1967); *Soviet J. Org. Chem.*, 3, 1758 (1967).

(201) H. Clement, *Bull. Soc. Chim. Fr.*, 5, 1011 (1938).

(202) K. N. Campbell, *J. Amer. Chem. Soc.*, 59, 1980 (1937).

(203) L. Gattermann, *Ann. Chem.*, 393, 215 (1912).

(204) Farbenfab. Bayer A.-G., German Patent 157,573 (1905); *J. Chem. Soc.*, 88, 355 (1905).

(205) L. Gattermann and F. Maffezzoli, *Chem. Ber.*, 36, 4152 (1903).

(206) D. N. Kursanov and R. R. Zel'vin, *Zh. Obshch. Khim.*, 9, 2173 (1939); *Chem. Abstr.*, 34, 4062 (1940).

(207) D. N. Kursanov and R. R. Zel'vin, *C. R. Acad. Sci. USSR*, 36, 17 (1942); *Chem. Abstr.*, 37, 1422 (1943).

(208) Reference 83, p 1241.

(209) L. Irrera, *Gazz. Chim. Ital.*, 62, 30 (1932).

(210) H. Meerwein, H. Disselnkoetter, F. Rappen, H. von Rintelen, and H. von deVloed, *Ann. Chem.*, 604, 151 (1957).

(211) H. Gross, A. Reiche, and E. Hoft, *Chem. Ber.*, 94, 544 (1961).

(211a) M. S. Newman and B. C. Ream, *J. Org. Chem.*, 31, 2175 (1966), and references therein.

(212) Reference 83, p 1189.

(213) U. Schoellkopf, J. Paust, A. Ali-Azrak, and H. Schumacher, *Chem. Ber.*, 99, 3391 (1966).

(214) U. Schoellkopf and E. Wiskott, *Ann. Chem.*, 694, 44 (1966).

(215) F. Adickes and G. Schaefer, *Chem. Ber.*, 65B, 950 (1932).

(216) H. Scheibler and H. Cobler, *ibid.*, 67B, 314 (1934).

(217) H. Scheibler, *ibid.*, 59B, 1022 (1926).

(218) H. Scheibler and G. Frikell, *ibid.*, 67B, 312 (1934).

(219) F. Adickes and P. P. Peckelhoff, *ibid.*, 68B, 1138 (1935).

cent work indicates a synchronous mechanism for the decomposition; no carbanionic intermediates could be trapped.[220]

b. Reaction with Chlorosulfonic Acid

Chlorosulfonic acid ($ClSO_3H$) converts formate esters into alkyl sulfonates (**109**) with loss of carbon monoxide and hydrogen chloride.[221–223] The reaction is very similar to that of formic acid and chlorosulfonic acid (section II.B.3.b). The

$$4 + HSO_3Cl \longrightarrow \underset{\mathbf{109}}{ROSO_3H} + CO + HCl$$

mechanism may similarly involve protonation of the ether oxygen, followed by loss of the incipient formylium ion.

c. Photolysis

In ultraviolet light formate esters produce carbon monoxide, carbon dioxide, hydrogen, alkane, the alcohol (**3**), alkene (**110**),

$$4 \xrightarrow{h\nu} CO + CO_2 + H_2 + RH + \underset{\mathbf{110}}{R'CH{=}CH_2} + 3$$

and a small amount of formaldehyde.[224–226] The decomposition is said to involve primarily the reaction yielding alkanol **3** and carbon monoxide *via* an intramolecular rearrangement.[225,226] The alkene (**110**) and formic acid are believed to come about *via* a second intramolecular rearrangement.[225,226] The other products arise from free radicals formed by three separate pathways.[224,225]

$$4 \xrightarrow{h\nu} H\overset{\overset{O}{\|}}{C}\cdot + RO\cdot \qquad (1)$$

$$4 \xrightarrow{h\nu} H\cdot + ROOC\cdot \qquad (2)$$

$$4 \xrightarrow{h\nu} HCOO\cdot + R\cdot \qquad (3)$$

d. Pyrolysis

Pyrolysis of formate esters over catalysts under conditions similar to those used for the decomposition of formic acid (section II.B.3) can take several courses depending on the nature of the ester. Methyl formate (**4**, R = CH_3) yields methanol (**3**, R = CH_3), methane, carbon monoxide, and carbon dioxide.[227,228] Higher alkyl formates with β hydrogens generally yield olefins (**110**) by formal loss of formic acid.[229] Simple decarbonylation sometimes accompanies this process, yielding the alcohol (**3**).[230]

Pyrolysis of triphenylmethyl formate (**4**, R = $C(C_6H_5)_3$) yields mainly triphenylmethane (**60**, Ar = C_6H_5; X = H) and some triphenylcarbinol (**60**, Ar = C_6H_5; X = OH)[231] by formal decarboxylation and decarbonylation, respectively. The mechanisms of these reactions are undoubtedly very similar to those described above for the photolytic decomposition.

3. Free-Radical Reactions

a. Chlorination

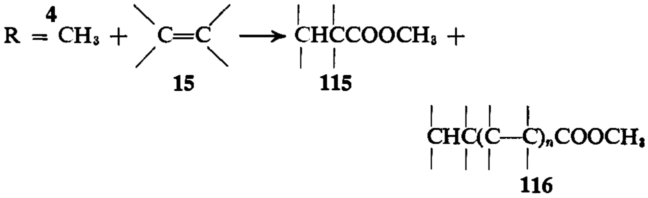
In ultraviolet light methyl formate gives rise to methyl chloroformate (**111**) and successively its mono- (**112**), di- (**113**), and trichloro (**114**) derivatives.[232] These hydrolyze to mixtures of

$$\underset{R\,=\,CH_3}{4} \xrightarrow[h\nu]{Cl_2} \underset{\mathbf{111}}{ClCOOCH_3} + \underset{\mathbf{112}}{ClCOOCH_2Cl} + \underset{\mathbf{113}}{ClCOOCHCl_2} + \underset{\mathbf{114}}{ClCOOCCl_3}$$

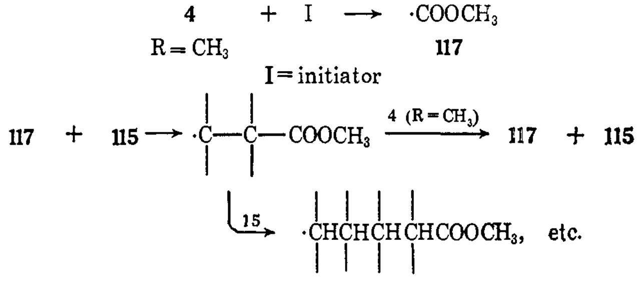
carbon monoxide, carbon dioxide, and hydrogen chloride; they saw use as war gases in World War I.[233]

b. Addition to Olefins

The reaction of formate esters with olefins (**15**) under free-radical conditions generally leads to mixtures of products resulting from abstraction of hydrogen atoms from the alcohol portion as well as the formyl hydrogen.[234] Thus, only methyl formate has seen much use in this application. In these reactions the 1:1 product (**115**) is formed in only moderate yields at best and is accompanied by telomers (**116**). Di-*t*-butyl peroxide and benzoyl peroxide have been used as initiators.[234–236]



The products are presumably formed *via* abstraction of the formyl protons to form radical **117**, which reacts with the olefin **15** to start a chain reaction, leading to the 1:1 adduct (**115**) and telomeric adducts (**116**).



c. Reaction with Hydrocarbons

Photochemical reaction of methyl formate and cyclohexane yields mainly cyclohexylcarbinol (**118**) and some bicyclohexyl (**119**).[237]

---

(220) J. C. Powers, R. Seidner, T. G. Parsons, and H. J. Berwin, *J. Org. Chem.*, 31, 2623 (1966).

(221) R. A. Dinerstein, U. S. Patent 2,595,341 (1949); *Chem. Abstr.*, 47, 1186 (1953).

(222) L. Bert and M. Procofieff, U. S. Patent 2,441,865 (1948); *Chem. Abstr.*, 42, 6375 (1948).

(223) Soc. d'Innov. Chim., British Patent, 601,602 (1948); *Chem. Abstr.*, 42, 8208 (1948).

(224) T. Tominaga, Y. Odaira, and S. Tsutsumi, *Technol. Rept. Osaka Univ.*, 14, 973 (1964); *Chem. Abstr.*, 62, 16043 (1965).

(225) P. Ausloos, *Can. J. Chem.*, **36**, 383 (1958).

(226) J. K. Royal and G. K. Rollefson, *J. Amer. Chem. Soc.*, **63**, 1521 (1941).

(227) E. Peytral, *Bull. Soc. Chim. Fr.*, 37, 562 (1925).

(228) P. Sabatier and A. Mailhe, *C. R. Acad. Sci., Paris, Ser. C*, **154**, 175 (1912).

(229) R. Delaby, *ibid.*, 176, 1898 (1923).

(230) R. Delaby and G. Moul, *Bull. Soc. Chim. Fr.*, **39**, 416 (1926).

(231) R. G. R. Bacon and J. Koechling, *J. Chem. Soc.*, 5609 (1964).

(232) V. Grignard, G. Rivat, and E. Urbain, *C. R. Acad. Sci., Paris, Ser. C*, 169, 1074 (1919).

(233) A. Kling, D. Florentin, A. Lassieur, and E. Schmutz, *ibid.*, **169**, 1166 (1919).

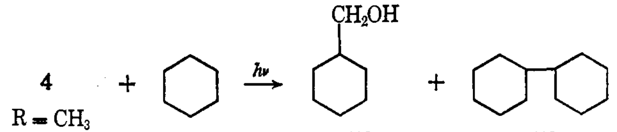
(234) W. H. Urry and E. S. Huyser, *J. Amer. Chem. Soc.*, **75**, 4876 (1953).

(235) A. D. Petrov, G. I. Nikishin, and V. D. Vorob'ev, *Fette, Seifen, Anstrichmittel*, 59, 1023 (1957); *Chem. Abstr.*, 53, 1127 (1959).

(236) D. D. Emrick and M. Darling, U. S. Patent 3,099,655 (1960); *Chem. Abstr.*, 60, 728 (1964).

(237) K. Shima and S. Tsutsumi, *Kogyo Kagaku Zasshi*, **64**, 1945 (1961); *Chem. Abstr.*, 57, 4218 (1962).

The data indicate that homolytic fission of the ester takes place to yield methoxy and formyl radicals (**120**). The latter give rise to formaldehyde, which abstracts a hydrogen atom to form radical **121**. Combination of **121** with cyclohexyl radicals then yields **118**. Bicyclohexyl (**119**) arises from cyclohexyl radicals in a secondary reaction.[237]



118 119

$$\underset{R\,=\,CH_3}{4} \xrightarrow{h\nu} CH_3O\cdot + \underset{120}{HCO\cdot} \longrightarrow HCHO \longrightarrow \underset{121}{\cdot CH_2OH}$$

V. Formamide

$HCONH_2$
122

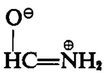
A. PHYSICAL PROPERTIES

Formamide is a colorless liquid with an ammoniacal odor. Being a very polar material (dielectric constant 109), it has a high boiling point, melts at 3°, and is completely soluble in water.

It is moderately toxic as an acute local hazard and a mild acute systemic hazard.[7] Its chronic effects are unknown.[7] When heated to decomposition (boiling point), it yields hydrogen cyanide.[7]

B. CHEMICAL PROPERTIES

1. Nucleophilic Reactions



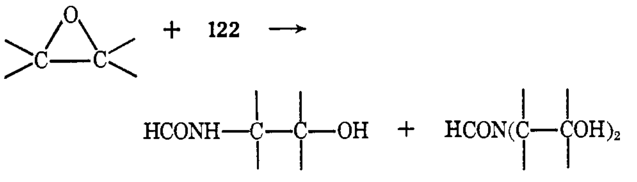
$$H\overset{O^{\ominus}}{C}{=}\overset{\oplus}{N}H_2$$

122a

The oxygen of formamide sometimes serves as a nucleophile as would be expected from resonance form **122a**. The amino group also is a nucleophilic moiety. Thus, formamide has two nucleophilic sites. Many of its nucleophilic reactions have been discussed with a view toward synthesis of various heterocyclic compounds.[238] Among these are reactions with amides, amines, ketones, halides, alcohols, Mannich bases, α,β-unsaturated ketones, dimethyl sulfate, orthoformates, and acid chlorides. The reader is referred to that review for a discussion of the above-mentioned reactions; only reactions not found there will be summarized in this paper.

a. Reaction with Epoxides

Formamide attacks the electrophilic centers of epoxides; mono- (**123**) and disubstituted (**124**) formamides are formed in moderate yield.[239,240] Acid catalysis promotes the formation of **124**, while basic catalysts raise the yield of **123**.[239] The reactions in acid undoubtedly involve protonated epoxide and those in base the ionized form (**93**, R_1 = H, R_2 = CHO) of formamide, whose pK_a is about 13.[241] This high acidity is due, in part, to a contributing resonance form of the anion similar to **122a**, in which the charge is shared by oxygen.

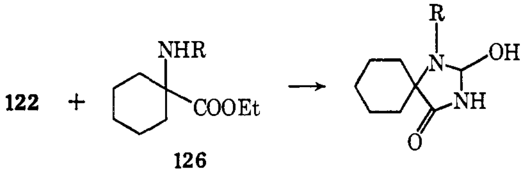


123 124

b. Reaction with Esters

In the presence of a basic catalyst, esters (**125**) are converted to amides (**75**, R = R′) by formamide (**122**).[242,243] Formate esters (**4**) are by-products. The reaction appears to involve formation of an intermediate N-acylformamide (**8**, R_1 = RCO; R_2 = H) by attack of the anion **93** (R_1 = H; R_2 = CHO) on the ester with displacement of an alkoxide ion (**94**). Attack on the formyl group by the alkoxide ion would then yield the products.[243] This proposal is supported by the isolation of product **127** from the reaction of substituted amino ester **126** and formamide.[244] This reaction evidently occurs by way of an N-acylformamide.

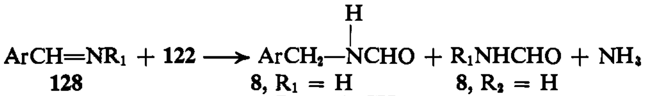
$$\underset{125}{R'COOR} + 122 \longrightarrow \underset{75,\ R\,=\,R'}{H_2NCOR'} + 4$$



126 127

c. Reaction with Imines and N,N′-Benzylidenebisamides

Schiff bases of aromatic aldehydes (**128**), when treated with formamide at 170°, undergo reductive cleavage yielding N-benzylformamides (**8**, R_1 = H; R_2 = $ArCH_2$), a formamide containing the R_1 group of the starting material, and ammonia.[245–247] Sometimes dibenzylformamides (**8**, R_1 = R_2 = $ArCH_2$) result[245,246] (compare section II.B.4.a).



$$\underset{128}{ArCH{=}NR_1} + 122 \longrightarrow \underset{\substack{8,\ R_1\,=\,H\\ R_2\,=\,ArCH_2}}{ArCH_2{-}\overset{H}{N}CHO} + \underset{8,\ R_2\,=\,H}{R_1NHCHO} + NH_3$$

Mechanistically, this reaction is believed to proceed by way of aldimine **128** (R_1 = H) by an amine–amide exchange. The aldimine is then reduced to primary amine **48** (R_3 = H; R_4 = Ar). Nucleophilic displacement of ammonia by formamide then yields the product **8** (R_1 = H_1; R_2 = $ArCH_2$).

---

(238) H. Bredereck, R. Gompper, H. G. v. Schuh, and G. Theilig, *Angew. Chem.*, 71, 753 (1959); *Newer Methods Prep. Org. Chem.*, 3, 241 (1964).

(239) L. P. Petrenko, *Tr. Voronezh. Univ.*, 42, 45 (1956); *Chem. Abstr.*, 53, 11208 (1959).

(240) F. G. Ponomarev, *Zh. Obshch. Khim.*, 22, 929 (1952); *Chem. Abstr.*, 47, 3794 (1953).

(241) J. Hine and M. Hine, *J. Amer. Chem. Soc.*, 74, 5266 (1952).

(242) N. Jochum, K. R. Riefstahl, and A. Tilly, German Patent 1,164,397 (1964); *Chem. Abstr.*, 60, 15742 (1964).

(243) E. L. Allred and M. D. Hurwitz, *J. Org. Chem.*, 30, 2376 (1965).

(244) E. Schipper, *Chem. Ind.* (London), 464 (1960).

(245) M. Sekiya and T. Fujita, *J. Pharm. Soc. Japan*, 71, 941 (1951); *Chem. Abstr.*, 46, 3983 (1952).

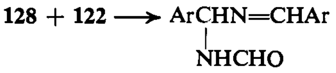
(246) M. Sekiya and S. Ishikawa, *Yakugaku Zasshi*, 78, 549 (1958); *Chem. Abstr.*, 52, 17244 (1958).

(247) M. Sekiya and T. Oishi, *Chem. Pharm. Bull.* (Tokyo), 7, 468 (1959).

$$\mathbf{128} + \mathbf{122} \longrightarrow \underset{\mathbf{128},\ R_1 = H}{ArCH{=}NH}$$

$$\underset{R_1 = H}{\mathbf{128}} \xrightarrow{[H]} \underset{\mathbf{48},\ R_3 = H;\ R_4 = ArCH_2}{ArCH_2NH_2} \longrightarrow \underset{\mathbf{8},\ R_1 = H;\ R_2 = ArCH_2}{ArCH_2NHCHO}$$

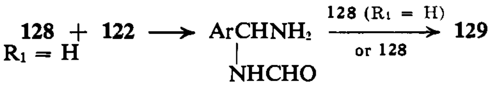
Certain oximes, which may be considered Schiff bases, are also converted to formamides in like manner[248] (see section V.B.2.c). At lower temperatures (100°) the above reaction of Schiff bases results in the formation of α-formylamino Schiff bases **129**,[247] presumably *via* addition of formamide to **128**



$$\mathbf{128} + \mathbf{122} \longrightarrow \underset{\displaystyle NHCHO}{ArCHN{=}CHAr}$$

129

(R_1 = H) followed by amine exchange of the resultant **130** with the aldimine **128** (R_1 = H) or **128** itself.[249,250] At higher temperatures compounds of structure **129** lead to N-benzylformamides (**8**, R_1 = H; R_2 = $ArCH_2$) by way of the N,N′-benzylidenebisamides (**73**, R = H), formed by nucleophilic displacement on aldimine **128** (R_1 = H) by formamide.[250] N,-N′-Benzylidenebisamides (**73**) are converted in about 50% yield to N-benzylformamides (**8**, R_1 = H; R_2 = $ArCH_2$) by heating at 170°, presumably through direct reduction[4] or reduction of the N-formylaldimine **128** (R_1 = CHO).[5]



$$\underset{R_1 = H}{\mathbf{128}} + \mathbf{122} \longrightarrow \underset{\displaystyle NHCHO}{ArCHNH_2} \xrightarrow[\text{or } \mathbf{128}]{\mathbf{128}\ (R_1 = H)} \mathbf{129}$$

130

$$\mathbf{129} + \mathbf{122} \longrightarrow \underset{\mathbf{73},\ R = H}{ArCH(NHCHO)_2} + \underset{R_1 = H}{\mathbf{128}}$$

$$\underset{\mathbf{73}}{ArCH(NHCOR)_2} \xrightarrow{[H]} \underset{\substack{\mathbf{8},\ R_1 = H_1 \\ R_2 = ArCH_2}}{ArCH_2NHCHO} + \mathbf{122}$$

For a discussion of possible modes of these reduction steps see the following section.

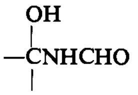
d. Reaction with Aldehydes and Ketones

N,N′-Benzylidenebisformamides (**73**, R = H) result in good yields (30–90%) from the reaction of benzaldehydes (**41**, R′ = Ar) and formamide (**122**) at about 100°.[251–254]

$$\underset{\mathbf{41},\ R' = Ar}{ArCHO} + \mathbf{122} \longrightarrow \underset{R = H}{\mathbf{73}}$$

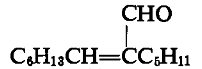
The reaction proceeds by attack of 2 moles of formamide on the carbonyl carbon with loss of a molecule of water, possibly *via* formation of an α-hydroxyformylamine (**131**). It appears that the N-benzylideneformamides (**128**, R_1 = CHO) are not involved (see below).

This reaction with aliphatic aldehydes has not been extensively studied. Heptaldehyde (**41**, R′ = n-C_6H_{13}), for example, is reported to yield only the dehydrated aldol condensation product **132**.[255] Formaldehyde, on the other hand, yields methylenebisformamide (**133**), when treated with 2 moles of formamide.[256,257] Two moles of formaldehyde and 1 mole of formamide combine to yield the dimethylol derivative **8** (R_1 = R_2 = CH_2OH).[258] Thus, formation of N,N′-alkylidenebisformamides is apparently not general with aliphatic aldehydes.



$$-\overset{\displaystyle OH}{\underset{|}{C}}NHCHO$$

131



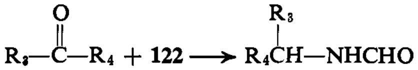
$$C_6H_{13}CH{=}\overset{\displaystyle CHO}{C}C_5H_{11}$$

132

$$HCHO + \mathbf{122} \longrightarrow \underset{\mathbf{133}}{CH_2(NHCHO)_2}$$

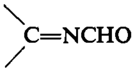
In contrast, at higher temperatures (170–230°) reaction of aldehydes (**41**) or ketones (**47**) with formamide leads to the formation of formamides **8** (R_1 = H; R_2 = R′) and **8** (R_1 = H; R_2 = $CH(R_3)R_4$), respectively.[99,259,260] Through catalysis by certain metals, the reaction may be carried out at lower temperatures (90–130°).[68]

$$\underset{\mathbf{41}}{R'CHO} + \mathbf{122} \longrightarrow \underset{\substack{\mathbf{8},\ R_1 = H \\ R_2 = R'}}{R'NHCHO}$$



$$\underset{\mathbf{47}}{R_3{-}\overset{\displaystyle O}{\overset{\|}{C}}{-}R_4} + \mathbf{122} \longrightarrow \underset{\substack{\mathbf{8},\ R_1 = H \\ R_2 = CH(R_3)R_4}}{R_4\overset{\displaystyle R_3}{C}H{-}NHCHO}$$

These examples are modifications of the Leuckart reaction (see section II.B.4.a). Their mechanism is still in doubt. Some workers have proposed formation of the addition compound **131** which could be reduced directly or *via* the dehydrated form **131a** to the observed products.[100,261,262] Others hold the view that formamide first dissociates to formic acid and ammonia, and that these primary products are the reactive species.[68,99,101,103] In view of the fact that N,N′-benzylidenebisformamides (**73**, R = H) can be converted to N-benzylformamides (**8**, R_1 = H; R_2 = $ArCH_2$) at 170° the Leuckart reaction of aldehydes has been suggested to occur through **73** (R = H) as described in section V.B.1.c.[5] Ketones might be converted to the observed formamides by reduction of the intermediate N-formylimine **131a**, formed by loss of water from **131**. In fact, efficient (92%) reduction of a compound of type **131a** by formamide at 170–180° has been reported.[263]



$$>C{=}NCHO$$

131a

---

(248) M. Sekiya and T. Oishi, *J. Pharm. Soc. Japan*. 73, 1017 (1953); *Chem. Abstr.*, **48**, 10663 (1954).

(249) M. Sekiya and A. Hara, *Chem. Pharm. Bull.* (Tokyo), 11, 901, (1963).

(250) M. Sekiya, A. Hara, K. Ito, J. Suzuki, and K. Tanaka, *ibid.*, **15**, 774 (1967).

(251) R. K. Mehre and K. C. Pandya, *Proc. Indian Chem. Soc.*, 10A, 279 (1939); *Chem. Abstr.*, 34, 1980 (1940).

(252) P. Agarwal, K. C. Pandya, and I. Tripathi, *J. Indian Chem. Soc.*, **21**, 383 (1944); *Chem. Abstr.*, **39**, 4595 (1945).

(253) G. C. Bhatnagar and K. C. Pandya, *Proc. Indian Acad. Sci.*, 24, 487 (1946); *Chem. Abstr.*, **41**, 3773 (1947).

(254) G. Thyagarajan and S. Naseem, *Indian J. Chem.*, 2, 251 (1964); *Chem. Abstr.*, **61**, 8229 (1964).

(255) M. Metayer and G. D. Bievre-Gallin, *C. R. Acad. Sci., Paris, Ser. C*, **225**, 635 (1947).

(256) C. W. Sauer and R. J. Bruni, *J. Amer. Chem. Soc.*, 77, 2559 (1955).

(257) P. Knudsen, *Chem. Ber.*, 47, 2698 (1914).

(258) S. L. Vail, C. M. Moran, and H. B. Moore, *J. Org. Chem.*, 27, 2067 (1962).

(259) O. Wallach, *Ann. Chem.*, **343**, 54 (1905).

(260) B. Schiedt, *J. Prakt. Chem.*, **157**, 203 (1941).

(261) W. H. Davies and M. A. T. Rogers, *J. Chem. Soc.*, 126 (1944).

(262) M. Mousseron, R. Jacquier, and R. Zagdoun, *Bull. Soc. Chim. Fr.*, 197 (1952).

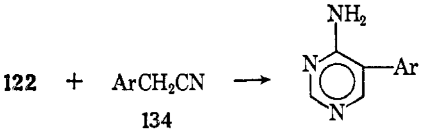
(263) A. Chatterjee and R. Raychaudhuri, *J. Org. Chem.*, **33**, 2546 (1968).

The mode of the latter reduction and that of imines or addition compounds of type **131** by formamide is still a subject of controversy. Some workers hold that formic acid, formed by the thermal decomposition[68,99,101,103] or hydrolysis[111,262] (by water formed in imine formation) of formamide, is the active reducing species. If the observation is accurate that ammonia and not carbon dioxide is principally evolved in the conversion of N,N'-benzylidenebisformamides (**73**, R = H) to N-benzylformamides (**8**, R_1 = H; R_2 = $ArCH_2$),[5] reduction by formic acid would seem unlikely. A counter-argument might be that carbon dioxide is soluble in these reaction mixtures. Alternatively, the autoxidation of imines of types **128** and **131a** has been proposed as the source of reduction, and the resinous by-products have sometimes been observed.[5] This would necessarily result in yields less than or equal to 50%, while better yields are often obtained. Others have suggested that the formyl group of formamide may serve as a hydride source[263] as does formic acid (section II.B.4). Support for this view derives from the fact that dimethylformamide (**8**, R_1 = R_2 = CH_3) serves as a hydride donor in a Lueckart-type reduction.[264] It appears obvious that more work is necessary before the detailed mechanistic aspects of this reaction are clear.

2. *Electrophilic Reactions*

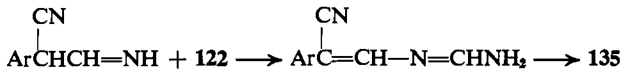
a. Reaction with Arylacetonitriles

5-Aryl-4-aminopyrimidines (**135**) result from condensation of formamide and arylacetonitriles (**134**),[265,266] although an earlier worker incorrectly attributed a 1,3,5-triazine structure to the products.[267,268] Without a catalyst low yields (10–20%) are obtained. Using ammonia as a catalyst about 50% yields result. The isolation of **136**,[265] formed by attack of the benzylic carbanion (resulting from proton removal from **134**) on formamide, implicates it as an intermediate. Nucleophilic attack of **136** or its tautomer with more formamide, followed by loss of water could yield **137**. Attack of the amino groups on the nitrile would lead to the product **135**, *via* tautomeric form **135a**.[265]

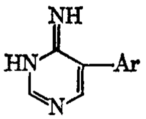


134

135



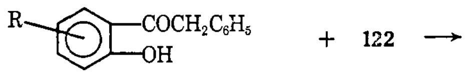
$$\underset{\mathbf{136}}{\mathrm{Ar\overset{CN}{\overset{|}{C}}HCH{=}NH}} + \mathbf{122} \longrightarrow \underset{\mathbf{137}}{\mathrm{Ar\overset{CN}{\overset{|}{C}}{=}CH{-}N{=}CHNH_2}} \longrightarrow \mathbf{135}$$



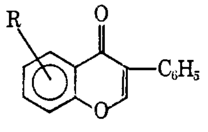
135a

b. Reaction with *o*-Hydroxyphenyl Benzyl Ketones

Isoflavones (**138**) can be prepared as a result of electrophilic attack of formamide on *o*-hydroxyphenyl benzyl ketones (**47**, R_3 = 2-HOC_6H_3R; R_4=$C_6H_5CH_2$), with loss of ammonia and water.[269,270] The reaction takes place in about 40% yield at reflux. Electrophilic attack of the formyl group of formamide on the phenolic oxygen is apparently the initial step.



47, R_3 = 2-HOC_6H_3R-*x*; R_4 = $C_6H_5CH_2$

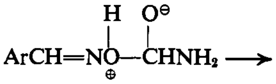


138

c. Dehydration of Aldoximes

Aldoximes are reportedly dehydrated to nitriles by the action of formamide at 140–170°. Only aromatic aldoximes (**128**, R_1 = OH) were tested, however.[271,272] Yields of **140** were 60–80%.

$\mathrm{ArCH{=}NOH} + \mathbf{122} \longrightarrow$
128, R_1 = OH



$$\mathrm{ArCH{=}\underset{\oplus}{N}\overset{H}{\overset{|}{O}}{-}\overset{O^{\ominus}}{\overset{|}{C}}HNH_2} \longrightarrow$$

139

$$\underset{\mathbf{140}}{\mathrm{ArCN}} + H_2O + \mathbf{122}$$

Conceivably the reaction involves electrophilic attack of the carbonyl group of formamide on the hydroxyl oxygen yielding an intermediate such as **139**. Elimination of the elements of water and formamide would yield the product. Other amides also may be used.

In contrast ketoximes apparently undergo hydrolysis to the ketone (**47**). The ketone undergoes reduction to the disubstituted formamide **8**, which is the product isolated[248] (see section IV.B.1.c).

d. Reaction with Grignard Reagents

Aldehydes do not result from treatment of formamide with Grignard reagents, although most other amides are converted to ketones[273] (yield 20–50%) in this way. Disubstituted formamides are reported to yield aldehydes.[274,319] With formamide itself, only the hydrocarbons derived from the Grignard reagents are formed.

3. *Free-Radical Reactions*

The formyl hydrogen of formamide can be abstracted in the same way as that in the formate esters (see section IV.B.3). The resultant carbamoyl radical (·$CONH_2$) takes part in free-radical reactions.

---

(264) E. C. Taylor and E. E. Garcia, *J. Amer. Chem. Soc.*, **86**, 4721 (1964).

(265) W. H. Davies and H. A. Piggot, *J. Chem. Soc.*, 347 (1945).

(266) J. Meseri, *Rev. Fac. Cienc. Quim. Univ. Nacl. La Plata*, **23**, 99 (1948); *Chem. Abstr.*, **48**, 10027 (1954).

(267) A. Novelli, *Anales Asoc. Quim. Arg.*, **31**, 23 (1943); *Chem. Abstr.*, **37**, 6668 (1943).

(268) A. Novelli, *Anales Asoc. Quim. Arg.*, **31**, 93 (1943); *Chem. Abstr.*, **38**, 364 (1944).

(269) J. E. Gowan, N. S. O'Connor, and T. S. Wheeler, *Chem. Ind.* (London), 1201 (1954).

(270) J. E. Gowan, M. F. Lynch, N. S. O'Connor, E. M. Philbin, and T. S. Wheeler, *J. Chem. Soc.*, 2495 (1958).

(271) S. Gabriel, *Chem. Ber.*, 36, 804 (1903).

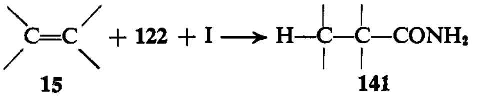
(272) M. Sekiya and K. Oishi, *J. Pharm. Soc. Japan*, **73**, 1243 (1953); *Chem. Abstr.*, **48**, 12701 (1954).

(273) C. Beis, *C. R. Acad. Sci., Paris, Ser. C*, **137**, 575 (1903).

(274) L. Bouveault, *Bull. Soc. Chim. Fr.*, **31**, 1322 (1904).

a. Addition to Olefins

By far the most widely studied free-radical reaction of formamide is its anti-Markovnikov addition to olefins (**15**) to yield carboxamides **141**. The reaction may be catalyzed by ultraviolet light,[275–282] peroxides,[283,284] or electron or γ rays.[285]



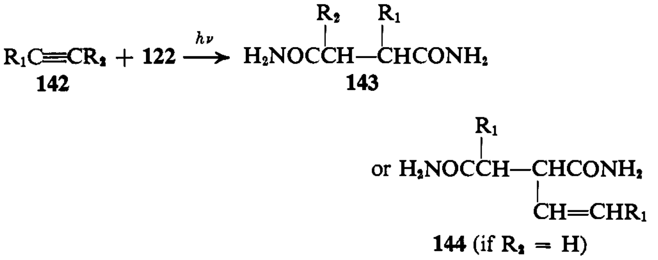
I = initiator

The photolytic reactions proceed in 50–90% yields, whereas the others are low conversion processes. Unsymmetrically substituted olefins yield mixtures of the two possible products. Under some conditions the reaction is stereospecific.[279]

The mechanism is very similar to that postulated in the free-radical addition of formate esters (**4**) to olefins (**15**) (section IV.B.3.b), except that telomerization is not as severe a side reaction.

b. Addition to Acetylenes

Photoamidation of acetylenes (**142**) with formamide has also been reported. Nonterminal acetylenes (**142**, R_1, $R_2 \neq H$) yield products resulting from the addition of 2 moles of formamide, namely **143**.[275] Terminal acetylenes (**142**, R_2 = H) react to form predominantly 2:2 adducts of structure **144**.[286]

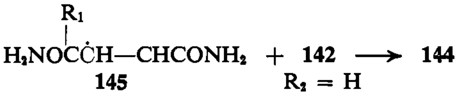


$$\underset{\mathbf{142}}{R_1C{\equiv}CR_2} + 122 \xrightarrow{h\nu} \underset{\mathbf{143}}{H_2NOC\overset{R_2}{\overset{|}{C}}H-\overset{R_1}{\overset{|}{C}}HCONH_2}$$

$$\text{or } H_2NOC\overset{R_1}{\overset{|}{C}}H-\underset{CH=CHR_1}{\underset{|}{C}}HCONH_2$$

144 (if R_2 = H)

The formation of **143** is analogous to the amidation of olefins, except that in the first step there is formed a substituted acrylamide, which subsequently undergoes amidation.[275] In the formation of **144** the intermediate substituted acrylamide undergoes addition of the carbamoyl radical, forming **145**, which reacts with more of the acetylene **142** (R_2 = H) to form

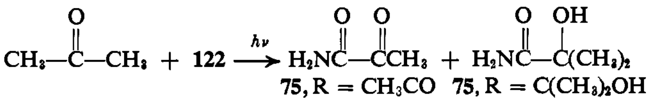


$$\underset{\mathbf{145}}{H_2NOC\overset{R_1}{\overset{|}{\dot{C}}}H-CHCONH_2} + \underset{R_2\,=\,H}{\mathbf{142}} \longrightarrow \mathbf{144}$$

the product **144**.[286]

c. Photochemical Reaction with Ketones

Ultraviolet irradiation of acetone and formamide yields **75** (R = CH_3CO) and **75** (R = $C(CH_3)_2OH$) in approximately equal amounts.[287] The formation of these products is easily



$$CH_3-\overset{O}{\overset{\|}{C}}-CH_3 + 122 \xrightarrow{h\nu} \underset{\mathbf{75},\,R\,=\,CH_3CO}{H_2N\overset{O}{\overset{\|}{C}}-\overset{O}{\overset{\|}{C}}CH_3} + \underset{\mathbf{75},\,R\,=\,C(CH_3)_2OH}{H_2N\overset{O}{\overset{\|}{C}}-\overset{OH}{\overset{|}{C}}(CH_3)_2}$$

rationalized on the basis of carbamoyl and acetyl radicals.[287]

4. *Decomposition Reactions*

a. Formation of Ammonia and Carbon Monoxide

Ammonia and carbon monoxide can be obtained from formamide by treatment with base and an alcohol (**3**) or phenol (**3**, R = Ar) at temperatures above 120°.[288,289] This reaction is envisioned as proceeding by reaction of the ionized form (**93**, R_1 = H; R_2 = CHO) of formamide and the alcohol to yield the ion **146** and ammonia. The latter, according to the proposal, decomposes to alkoxide **94** and carbon monoxide.[288]

$$122 + \underset{\mathbf{93},\,R_1\,=\,H;\ R_2\,=\,CHO}{{}^{\ominus}NHCHO} \xrightarrow[(3)]{ROH} NH_3 + \underset{\mathbf{146}}{{}^{\ominus}COOR} \longrightarrow \underset{\mathbf{94}}{RO^{\ominus}} + CO$$

However, by analogy with the decomposition of formate esters (section IV.B.2.a), one might expect this decomposition to be a synchronous process with no carbanionic species involved.

Reaction of formamide with chlorosulfonic acid or thionyl chloride at room temperature also results in the formation of ammonia and carbon monoxide.[290] Protonation (or in the case of thionyl chloride complexation) of the nitrogen and unimolecular decomposition is probably the pathway of this reaction.

b. Formation of Hydrogen Cyanide

Dehydration of formamide by heating over a metallic catalyst at elevated temperatures (350–600°) at either ambient[291,292] or reduced pressures[293,294] results in good yields of hydrogen cyanide. A free-radical chain mechanism with hydrogen atoms as chain transfer agents has been suggested.[295]

c. Formation of Isocyanate Ion

The potassium salt (**93**, R_1 = H; R_2 = CHO) of formamide when heated in a dry state gives hydrogen and potassium isocyanate.[296] Thus, this ion like the formate ion (**2**) seems to be capable of acting as hydride donor at elevated temperatures.

---

(275) D. Elad, *Proc. Chem. Soc.*, 225 (1962).

(276) D. Elad, *Chem. Ind.* (London), 362 (1962).

(277) D. Elad, Israeli Patent 16,689 (1963); *Chem. Abstr.*, **61**, 8195 (1964).

(278) D. Elad and J. Rokach, *J. Org. Chem.*, **29**, 1855 (1964).

(279) D. Elad and J. Rokach, *J. Chem. Soc.*, 800 (1965).

(280) D. Elad and J. Rokach, *J. Org. Chem.*, **30**, 3361 (1965).

(281) D. Elad, *Angew. Chem. Int. Ed. Engl.*, **5**, 255 (1966).

(282) M. Fisch and G. Ourisson, *Bull. Soc. Chim. Fr.*, 1325 (1966).

(283) A. Rieche, E. Schmitz, and E. Gruendemann, *Z. Chem.*, **4**, 177 (1964).

(284) A. Rieche, E. Schmitz, and E. Gruendemann, *Angew. Chem.*, **73**, 621 (1961).

(285) J. Rokach, C. H. Krauch, and D. Elad, *Tetrahedron Lett.*, 3253, (1966).

(286) G. Friedman and A. Komem, *ibid.*, 3357 (1968).

(287) H. Grossmann, *Z. Naturforsch.*, **20b**, 109 (1965).

(288) T. Enkvist, H. Merikoski, and P. Tikkanen, *Chem. Ber.*, **72B** 1717 (1939).

(289) T. Enkvist and A. Kurkula, *ibid.*, **73B**, 1253 (1940).

(290) L. Bert, *C. R. Acad. Sci., Paris, Ser. C*, **222**, 666 (1946).

(291) E. Asendorf and F. Bittner, U. S. Patent 2,904,400 (1959); *Chem. Abstr.*, **54**, 3879 (1960).

(292) L. Fallows and E. V. Mellers, British Patent 584,598 (1947); *Chem. Abstr.*, **41**, 3267 (1947).

(293) T. Hatano, Japanese Patent 2664 (1956); *Chem. Abstr.*, **51**, 10015 (1957).

(294) H. G. Schwarz, R. Luehdemann, and E. Hartert, German Patent 1,209,561 (1966); *Chem. Abstr.*, **64**, 10803 (1966).

(295) N. W. Luft, *Monatsh.*, **86**, 671 (1955).

(296) E. C. Franklin, *J. Amer. Chem. Soc.*, **55**, 4915 (1933).

VI. Monosubstituted Formamides

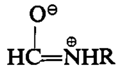
RNHCHO
147

A. PHYSICAL PROPERTIES

The simple monosubstituted formamides (**147**) are high-boiling, water-soluble liquids. They possess a very slight amine-like odor. No published toxicity data are available on these materials.

B. CHEMICAL PROPERTIES

1. *Nucleophilic Reactions*



$$H\overset{O^{\ominus}}{\overset{|}{C}}{=}\overset{\oplus}{N}HR$$

147a

The monosubstituted formamides, like formamide, are nucleophilic, both at nitrogen and oxygen as would be expected from a consideration of resonance form **147a**. They undergo many reactions in direct analogy with formamide itself.

a. Vilsmeier Reaction

Formylation by reaction of formamides and aromatic or olefinic compounds in the presence of phosphorus oxychloride is known as the Vilsmeier reaction. This reaction has been reviewed.[297] Compounds of general structure **148** (X = $POCl_2$) are believed to be the reactive intermediates and are collectively referred to as Vilsmeier adducts. They are formed by the nucleophilic attack of the oxygen of the monosubstituted formamides on the reagent XCl. A variety of these are known. Their use as synthetic intermediates is reviewed in the following sections.

$$R\overset{\oplus}{N}H{=}CHOX$$

148

b. Formation of Isonitriles and Their Dihalides

Reaction of monosubstituted formamides (**147**) with Lewis acid dehydrating agents such as phosphorus oxychloride ($POCl_3$) in the presence of a base yields isonitriles (**149**). These reactions have been reviewed,[298] as well as some of the reactions of this interesting class of compounds.[299] Treatment of monosubstituted formamides simultaneously with a dehydrating agent (such as thionyl chloride) and a halogenating agent (*e.g.*, chlorine) yields isonitrile dihalides (**150**). A survey of this technique already has been published.[300,301] The dihalides **150** also appear to have useful synthetic potential.

$$\mathbf{147} \longrightarrow \underset{\mathbf{149}}{RN{\equiv}C} + H_2O$$

$$\mathbf{147} + (X_2) \xrightarrow{-H_2O} \underset{\mathbf{150}}{RN{=}CX_2}$$

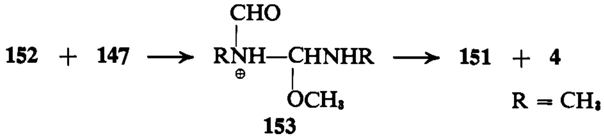
The first step in both of these reactions involves nucleophilic attack of the formyl oxygen of **147** on the Lewis acid to yield a species such as **148** (X = $POCl_2$, SOCl) which undergoes an α-elimination reaction, forming **149**.

c. Formation of Formamidinium Salts

Some monosubstituted formamides may be converted to the corresponding formamidinium salts **151** and the imines **152** by treatment with dimethyl sulfate.[302,303]

$$\mathbf{147} \xrightarrow{(CH_3)_2SO_4} \underset{\mathbf{151}}{RNHCH{=}\overset{\oplus}{N}HR} + \underset{\mathbf{152}}{R\overset{\oplus}{N}H{=}CHOCH_3}$$

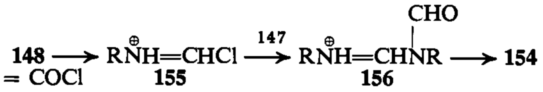
The imine **152** is probably an intermediate in the formation of **151**. Nucleophilic attack of **147** on **152** would yield **153** and thence **151** by elimination of methyl formate (**4**, R = CH_3).[304]



$$\mathbf{152} + \mathbf{147} \longrightarrow \underset{\mathbf{153}}{R\overset{\overset{CHO}{|}}{\underset{\oplus}{N}}H{-}\underset{\underset{OCH_3}{|}}{C}HNHR} \longrightarrow \mathbf{151} + \mathbf{4} \qquad R = CH_3$$

Reaction of **147** and phosgene similarly leads to the formamidinium salt **154**. Presumably **148** (X = COCl) loses carbon dioxide to yield **155**. Nucleophilic attack by the nitrogen atom of **147** might then lead to **156**. Reaction of the formyl group of **156** with another mole of phosgene followed by loss of carbon dioxide would yield the product **154**.[304]

$$\mathbf{147} \xrightarrow{COCl_2} \underset{\mathbf{154}}{Cl_2CH\overset{\overset{R}{|}}{N}CH{=}\overset{\oplus}{N}HR}$$



$$\underset{X\,=\,COCl}{\mathbf{148}} \longrightarrow \underset{\mathbf{155}}{R\overset{\oplus}{N}H{=}CHCl} \xrightarrow{\mathbf{147}} \underset{\mathbf{156}}{R\overset{\oplus}{N}H{=}CH\overset{\overset{CHO}{|}}{N}R} \longrightarrow \mathbf{154}$$

When R = alkyl, compound **154** is relatively stable, but when R = aromatic, loss of hydrogen chloride and carbon monoxide occurs readily and formamidinium salt **151** (R = Ar) is formed.[304]

d. Reaction with Epoxides

The formyl derivatives of primary amines readily react with epoxides. This is demonstrated by the formation of **124** from **123** in the reaction of formamide and an epoxide[112] (section V.B.1.a).

e. Reaction with Esters

In the presence of base, monosubstituted formamides react with esters (**125**), forming good yields of the corresponding amides (**157**) and the formate ester (**4**), presumably *via* anion **93** (R_1 = CHO; R_2 = R).[242,243]

$$\underset{\mathbf{125}}{R'COOR} + \mathbf{147} \longrightarrow \underset{\mathbf{157}}{R'CONHR} + \underset{\mathbf{4}}{HCOOR}$$

f. Reaction with Aldehydes and Ketones

Monosubstituted formamides (**147**) and formaldehyde combine to yield methylols **158** in analogy with formamide (**122**).[258,305]

---

[297] Reference 83, p 1211.

[298] I. Ugi, U. Fetzer, U. Eholzer, H. Knupfer, and K. Offermann, *Angew. Chem. Int. Ed. Engl.*, 4, 472 (1965).

[299] I. Ugi, *ibid.*, 1, 8 (1962).

[300] E. Kuhle, *ibid.*, 1, 647 (1962).

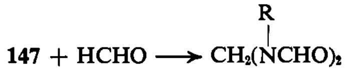
[301] E. Kuhle, B. Anders, and G. Zumach, *ibid.*, **6**, 649 (1967).

[302] H. Bredereck, R. Gompper, K. Klemm, and H. Rempfer, *Chem. Ber.*, **92**, 837 (1959).

[303] H. Bredereck, F. Effenberger, and E. Henseleit, *ibid.*, **98**, 2754 (1965).

[304] W. Jentzsch, *ibid.*, 97, 1361 (1964).

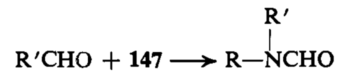
[305] R. Stroh and H. Haber, German Patent 923,485 (1955); *Chem. Abstr.*, 52, 2053 (1958).



$$147 + HCHO \longrightarrow CH_2(\overset{R}{N}CHO)_2$$

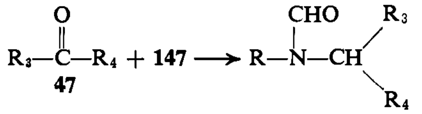
158

Some monosubstituted formamides have seen limited use in the Leuckart reaction of aldehydes and ketones.[99,262,306–308] Formamides of secondary amines result.



$$R'CHO + 147 \longrightarrow R\text{—}\overset{R'}{N}CHO$$

41 **8**, $R_1 = R$, $R_2 = R'$



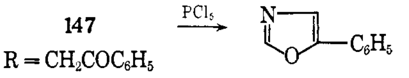
47

8, $R_1 = R$, $R_2 = CH(R_3)R_4$

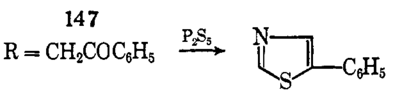
Mechanistically the reaction cannot involve formation of imine **131a**, although enamine formation is conceivable. This reaction therefore cannot involve autoxidation of an imine as has been suggested for the Leuckart reaction using formamide (section V.B.1.d). This conclusion has led to the suggestion[99,135] that dissociation of the formamide to the amine and formic acid occurs on the basis of the observation that disubstituted formamides will undergo the reaction.[262,308] However, this interpretation has been disputed.[262,308] This question will require further investigation before it can be satisfactorily resolved. More than likely several mechanistic pathways are involved in the Leuckart reaction.

g. Formation of Heterocyclics

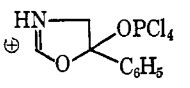
The nucleophilic nature of the formyl oxygen of monosubstituted formamides has been used to effect intramolecular cyclizations. For example, treatment of formamide **147** ($R = CH_2COC_6H_5$) with phosphorus pentachloride results in the formation of 5-phenyloxazole (**159**). Treatment with phosphorus pentasulfide yields 5-phenylthiazole (**160**).[309] The former reaction undoubtedly involves nucleophilic attack on the complexed ketone carbonyl by the formyl oxygen to yield an intermediate such as that conceptualized in **161**. Loss of the elements of phosphorus oxychloride and hydrogen chloride would then yield **159**. The reaction involving phosphorus pentasulfide is probably very similar, but involves initial formation of a thioformamide.



159

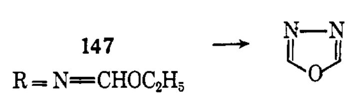


160



161

Alkoxides (**94**) have also been displaced in a similar manner. 1,3,4-Oxadiazole (**162**) can be synthesized from the substituted formamide **147** ($R = N{=}CHO_2H_5$), by displacement of ethoxide (**94**, $R' = C_2H_5$).[310]

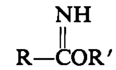


162

h. Reaction with Alkyl Halides

Disubstituted formamides (**8**) can be prepared in good yield by treatment of monosubstituted formamides (**147**) with alkyl halides (**163**) and sodium hydride. Anion **93** ($R_1 = R$; $R_2 = CHO$) is the nucleophile.[220] Conversion of the anion to the corresponding silver salt can be accomplished by treatment with silver nitrate.[311] This silver salt upon treatment with an alkyl halide yields both O- and N-alkylation products, **164** and **8**, respectively. The ratio of these products varies with substituent, conditions, and alkyl halide.[311,311a,b] Formation of **164** indicates considerable sharing of the negative charge by the oxygen, as indicated by resonance form **147a** of the starting material.

$$\underset{\mathbf{163}}{147 + R'X} \xrightarrow{NaH} 8$$

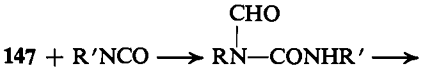


$$R\text{—}\overset{\overset{NH}{\|}}{C}OR'$$

164

i. Reaction with Isocyanates

Monosubstituted formamides reportedly react with isocyanates (**165**), forming formamidines **168**.[312,313] Loss of carbon dioxide from the urethane **167** formed by rearrangement of the initial adduct **166** is the proposed mechanistic rationale for this transformation.[313]



$$147 + R'NCO \longrightarrow R\overset{CHO}{N}\text{—}CONHR' \longrightarrow$$

165 **166**

$$RN{=}CHOCONHR' \longrightarrow RN{=}CHNHR'$$

167 **168**

2. Electrophilic Reactions

The carbonyl carbon of monosubstituted formamides is subject to attack by nucleophiles, and these compounds undergo many of the same electrophilic reactions as formamide itself.

a. Reaction with *o*-Hydroxyphenyl Benzyl Ketones

Isoflavones (**138**) result from reaction of monosubstituted formamides (**147**) and *o*-hydroxyphenyl benzyl ketones (**47**, $R_3 = 2\text{-}HOC_6H_3R\text{-}x$; $R_4 = C_6H_5CH_2$).[270] Yields (25–60%) are

---

(306) W. Speer, U. S. Patent 2,108,147 (1938); *Chem. Abstr.*, 32, 2542 (1938).

(307) M. Metayer, *Bull. Soc. Chim. Fr.*, 1050 (1950).

(308) M. Mousseron, R. Jacquier, and R. Zagdoun, *ibid.*, 974 (1953).

(309) M. Bachstez, *Chem. Ber.*, 47, 3163 (1914).

(310) C. Ainsworth, *J. Amer. Chem. Soc.*, 87, 5800 (1965).

(311) A. W. Titherly, *J. Chem. Soc.*, 71, 467 (1897).

(311a) H. L. Wheeler and T. B. Johnson, *ibid.*, 73, 136 (1900).

(311b) A. Furth, *Monatsh.*, 23, 1154 (1902).

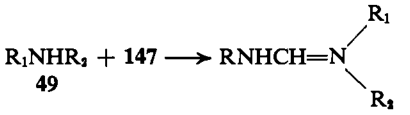
(312) W. Logemann, D. Artini, and G. Tosolini, *Chem. Ber.*, 91, 2566 (1958).

(313) W. Logemann and D. Artini, *ibid.*, 91, 2574 (1958).

superior to those obtained with formamide. The reaction is analogous except that 2 moles of alcohol (**3**) are eliminated instead of water.

b. Reaction with Amines

Substituted formamides react with amines (**49**) with elimination of water to form imino compounds of type **169**. In this



$$R_1NHR_2 + \mathbf{147} \longrightarrow RNHCH{=}N(R_1)(R_2)$$

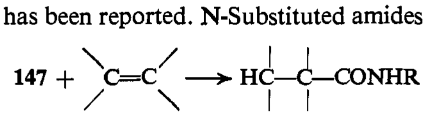
49 **169**

way heterocyclic compounds have been synthesized, *e.g.*, triazoles[314] and imidazoles.[20-22]

3. Free-Radical Reactions

Free-radical reactions of monosubstituted formamides have not been studied in detail, probably owing to the possibility of reaction at the substituent as well as the formyl group.

Addition to olefins (**15**) under the influence of ultraviolet light[276, 277] has been reported. N-Substituted amides **170** result.



15 **170**

Mechanistically the reaction is analogous to that involving methyl formate (**4**, R = CH_3) (see section IV.3.b).

4. Decomposition Reactions

Thermal decomposition of monosubstituted formamides over metallic catalysts comprises a synthesis of nitriles (**171**). Temperatures of 400–500 are employed.[315-318] In some cases reduced pressure is used.[318] Yields are of the order of 60%. By-

$$\mathbf{147} \longrightarrow \mathbf{149} \longrightarrow RCN$$

171

products include carbon monoxide, carbon dioxide, hydrogen, water, and the parent amine (**49**, R_1 = H; R_2 = R), which may be recycled.

Rationalization of the reaction is based on formation of the isonitrile (**149**) by dehydration. Rearrangement of the latter then yields the nitrile (**171**). The by-products are thought to result from direct decarbonylation of the formamide, hydrolysis of the formamide by water formed in the dehydration, and decomposition of the formic acid formed[315] (see section II.B.3.a,b).

VII. Disubstituted Formamides

Disubstituted formamides are very versatile both as solvents and chemical reagents. Their chemistry and utility are exemplified by the simplest member of the series, dimethylformamide (**8**, R_1 = R_2 = CH_3). A very recent publication[319] is a comprehensive reference on the chemistry of this compound and the reader is referred to it for detailed discussion.

Acknowledgment. The author thanks Drs. Fred Stone and Dale McKenzie for encouragement in this undertaking, Dr. McKenzie for reading and commenting on the manuscript, Miss Diane Ainsworth for typing it, and Union Carbide Corporation for facilities used in its preparation.

---

(314) C. F. Allen and A. Bell, ref 17, p 96.

(315) A. Mailhe, *C. R. Acad. Sci., Paris, Ser. C*, **176**, 689 (1923).

(316) A. Mailhe, *ibid.*, **176**, 1159 (1923).

(317) O. Nicodemus, German Patent 482,943 (1926); *Chem. Abstr.*, **24**, 626 (1930).

(318) W. Muench, E. Ruoti, C. Maderno, and G. Silverstri, U. S. Patent 2,904,579 (1959); *Chem. Abstr.*, **54**, 2269 (1960).

(319) R. S. Kittila, "Dimethylformamide, Chemical Uses," E. I. du Pont de Nemours and Co., Wilmington, Del., 1967.