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ACETIC FORMIC ANHYDRIDE

A REVIEW

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CONTENTS

INTRODUCTION

The goal of this Report is that of collecting all available published data on the properties, reactivity and applications of acetic formic anhydride (AFA, **1**). The Report is exhaustive and contains literature coverage through June 1988. A recent review by Olah[96] deals less specifically with formylating agents.

1. PHYSICO-CHEMICAL PROPERTIES AND STRUCTURAL ASPECTS

Physical data on **1** and other formic anhydrides are very scant. No accurate data about vapour pressure and heats of vaporization are available.

The simplest member of the formic anhydride series, formic anhydride, is a liquid [reported boiling points are: 26–27°C at 3600 Pa (a fraction with ca 90% mol/mol titre)[111] and 27°C at 3733 Pa (91% purity)[24]]. It is known to decompose to carbon monoxide and formic acid at room temperature with a time constant of 1 h.[82] Even trap to trap distillation at ca −10°C under 'reduced' pressure gave mixtures of formic anhydride and formic acid.

Acetic formic anhydride (**1**), is a colorless lachrymatory liquid, b.p. 29°C (2267 Pa)[17] (Table 1). The melting point of AFA as well as its free energy of formation, the free energy of decomposition

Table 1. Some reported boiling points of AFA

T (°C)	P (Pa)	Refs
27–28	1333	35
25.5–26.5	1333	55
27–28	1333	80
29*	2267	17
32*	2267	48
35–36	2666	122
35	3200	112
105–120*	101325	17

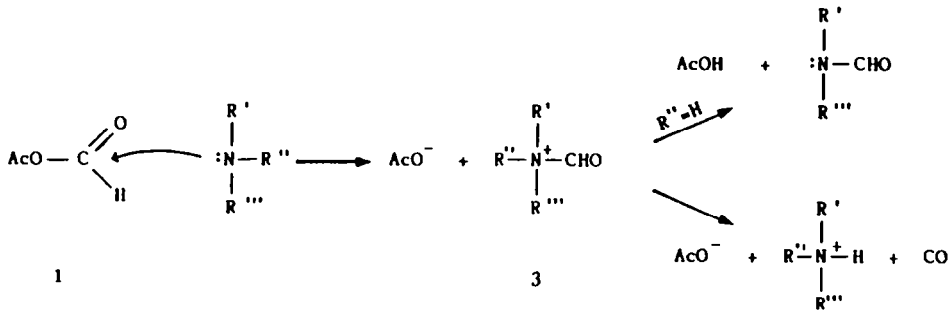
*From distillation of formic acid–acetic anhydride mixture (FAM, 2, see Section 5).

to acetic acid and carbon monoxide[110] and its 'spontaneous' decomposition rate constant are not known. In fact, **1** is somewhat unstable and decomposes slowly at room temperature, but much faster above 60°C. A sealed sample was reported to have exploded after two weeks because of CO evolution.[90] For this reason AFA should be stored at 4°C in an unsealed standard round bottom flask fitted with a polyethylene stopper.[80]

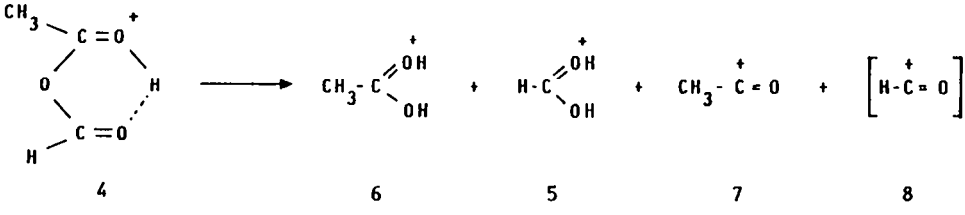
$$\underset{\mathbf{1}}{CH_3COO\text{–}CHO} \xrightarrow{\Delta} CH_3COOH + CO$$

The decomposition of **1** is accelerated by sodium acetate[110] or pyridine.[17,90,110] Decomposition depends upon the solvent: it is very fast in toluene, carbon tetrachloride, nitrobenzene and benzaldehyde, moderate in benzene and acetone, slow in ethanol, 1-pentanol and isobutanol and imperceptible in carbon disulfide and ether.[110] This reaction is catalyzed by some strong tertiary nitrogen bases such as N,N-dimethylbenzeneamine, brucine, strychnine and nicotine whereas the action of quinine, morphine, quinoline and papaverine is very weak. It was found that neither primary nor secondary bases acted similarly and other compounds with less basic character did not cause the liberation of carbon monoxide.[110]

A possible mechanism for the decomposition by tertiary bases requires an attack by the base on the formyl carbonyl of **1** with formation of the positively charged formyl base **3** and the counterion acetate; analogously to the similar reaction between pyridine and acetic anhydride.[44] Now, if the formylated base **3** is primary or secondary, it will recover its lone pair simply by transferring its proton to another molecule of base or acetate leading to substitution, whereas, if there are no hydrogen atoms available on the nitrogen, it will recover its neutrality by transferring the formyl proton with evolution of CO.



The acids (sulfuric, nitric, hydrofluoric, hydrochloric and, to a lesser extent, phosphoric) also catalyze this reaction. Hydrofluoric acid and **1** at 0°C and atmospheric pressure produced a mixture of formyl fluoride, acetyl fluoride and the corresponding acids. The reaction, depending on relatively minor variations of conditions, may yield equimolar amounts of the formyl halides or almost solely formyl fluoride (61%).[95] On the other hand concentrated acetic acid did not cause evolution of CO,[110] therefore, in the preparation of **1** from acetic anhydride and concentrated formic acid, it is reasonable to conclude that the observed partial decomposition of **2** is due to formic acid. Olah and Dunne observed[94] some evolution of CO upon protonation of **1** in superacid medium at low temperature (−80°C): an excess of FSO_3H–SbF_5–SO_2 solution cleaved the protonated anhydride (**4**) to protonated formic (**5**) and acetic (**6**) acids plus the acetyl cation (**7**). Formyl cation (**8**) was not observed, because it decomposed as soon as it was formed. The cleavage of the mixed anhydride under these conditions was rationalized in terms of a further protonation on the ether oxygen (the



remaining lone pair of the carbonyl oxygens was already coordinated in the first protonation, which occurs even at low concentrations of superacid medium): the charge–charge repulsion destabilizes this diprotonated species causing the cleavage. By treating AFA with an equimolar amount of superacid solution only the monoprotonated species (**4**) was obtained: it underwent a rapid inter- and intra-molecular proton exchange, as shown by the PMR spectroscopy (Fig. 1).[94]

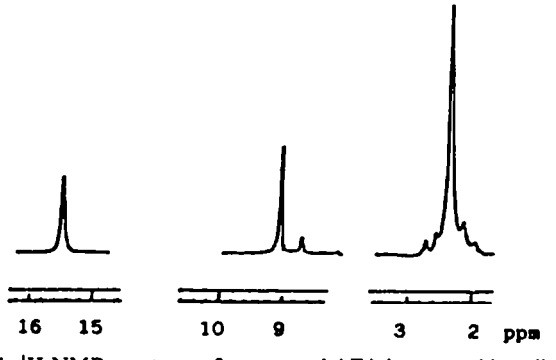


Fig. 1. ^{1}H-NMR spectrum of protonated AFA in superacid medium.[94]

Acetic formic anhydride was found to be a non planar molecule, by gas phase electron diffraction studies.[146] The formyl and the acetyl fragments are twisted out of the C—O—C plane by 21° and 46°, respectively, giving a dihedral angle of 126° between the two moieties. The formyl C—H and the acetyl C=O bonds are nearly parallel (Fig. 2) making an asymmetric structure like formic

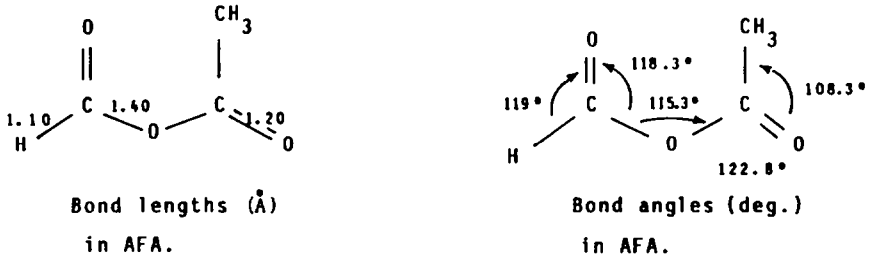


Fig. 2. Structure and structural parameters of acetic formic anhydride.[146]

anhydride,[24] but differing from that of acetic anhydride, which has a symmetrical structure. Further torsional vibrations around C—O are wider in the molecule of **1**. The origin of these conformational differences is not clear; resonance and a more favourable intramolecular carbonyl dipole–dipole interaction might be held responsible for this difference. The resonance energy of **1** has not been determined whereas that of acetic anhydride is reported to be about 30 kcal mole^{-1}.[152] There is no evidence of any intramolecular O···H bond and the calculated O···H distance is 2.7 Å, which nearly equals the sum of the Van der Waals radii of hydrogen and oxygen atoms.[145] By and large this molecule shows a stiffer conformation than that of acetic anhydride (Table 2).

Table 2. Structural parameters* for acetic, acetic formic and formic anhydrides[24]

	Acetic	Acetic formic[146]	Formic
	Bond lengths (Å)		
C—O	1.405(1)	1.397(1)	1.384(3)
C=O	1.183(1)	1.195(1)	1.188(2)
C—H	—	1.10	1.10
	Bond angles (degrees)		
(C—O—C)	115.8(8)	115.3(5)	115(2)
(O—C=O)[a]	121.7(2)	122.8(4)	—
(O—C=O)[b]	—	118.3(5)	123.4(5)
(O—C—H)	—	119(13)	119.1(9)
(O—C—C)	108.3(2)	108.3	—
	Torsional angle around C—O bond (degrees)		
formyl C—O	—	25(20)	17(6) 26(9)
acetyl C—O	48.5(8)	39(24)	—

* Estimated standard deviations in parentheses.
[a] Acetyl moiety.
[b] Formyl moiety.

The sigmatropic isomerization (migration of the acetyl group from one oxygen to the other) of **1** was theoretically studied by the MINDO/3 method. The calculated enthalpy of activation of the process is 200.9 kJ mole^{-1} and lies at the limits of the scale for tautomeric reactions.[118]

2. SPECTROSCOPIC STUDIES

2.1. *Infrared spectroscopy*

An accurate determination of infrared absorption bands of **1** and their assignments was performed by Vledder *et al.* in 1970 on pure mixed anhydride samples.[145] The normal coordinate calculations were carried out with Wilson's GF formalism (Table 3).

Table 3. Vibrational spectroscopic study of **1** in a CCl_4 solution[145]

Frequency Raman bands (cm^{-1})	IR bands (cm^{-1})	Assignments
1789	1794	stretching C=O formyl
1765	1775	stretching C=O acetyl
1432	1427	CH_3 asym stretching oop
1373	1373	CH_3 sym stretching oop
1200	1194	CH_3 asym bending ip
1184	1183	CH_3 sym bending ip
1046	1038	C—H bending
928	925	CH_3rocking oop
648	635*	COO formyl bending
557	556*	OCC bending

* Pure liquid, measured in a 0.012 mm KBr cell.
ip: in plane; oop: out of plane.

A comparison of the spectra of **1** and its mono and trideutero analogues in the region between 3200 and 2000 cm^{-1} led to the conclusion that the formyl C—H stretching frequency nearly fitted with the methyl mode at 2990 cm^{-1}, the formyl stretching was found at 2256 cm^{-1} in monodeutero **1**. The remaining absorptions are probably due to overtones and combination bands. The region between 2000 and 1500 cm^{-1} is the most characteristic: the carbonyl shows two peaks (1784 and 1779 cm^{-1}) with an unusually small splitting of about 20 cm^{-1} considerably less than the value of about 60 cm^{-1} found for symmetrical anhydrides.[18] This splitting increases to about 35 cm^{-1} in the monoformyl and fully deuterated forms. From the differences noted in the spectrum the authors concluded that the 1775 cm^{-1} band is mainly due to stretching vibration contributions of the formyl carbonyl whereas the lower frequency was assigned to an out of plane (oop) mode of vibration. The two deformation frequencies of the methyl group are to be found at about 1378 (symmetric) and 1450 cm^{-1} (antisymmetric); the antisymmetric should be doubly degenerate. As a consequence the two bands at 1432 and 1373 cm^{-1} were readily assigned to these vibrations; the doubly degenerate band could not be resolved. The formyl C—H deformation could also fall in this region (precisely at 1370 cm^{-1}). The situation in the next region (1250–1750 cm^{-1}) is complicated because large interactions are known to occur between formyl and acetyl C—O and C—C bonds: all compounds (deuterated as well as undeuterated) showed two bands at about 1190 and 900 cm^{-1}; both were relatively insensitive to deuteration. They were assigned to acetyl C—O, formyl C—O and C—C stretching respectively. The 1038 cm^{-1} band was attributed to the methyl rocking mode by comparison with the bands of mono and trideutero compounds. Finally the 557 cm^{-1} band should mainly be due to the C—H oop bending of the formyl group. The Raman spectrum of **1** was also recorded (Table 3) and no significant differences were observed. The force constants associated with C—H and C=O stretching and bending are all quite normal, a fact implying the absence of any intramolecular hydrogen bond.[145]

The IR spectrum of equilibrated FAM at 45°C in $CHCl_3$ (Fig. 3) was recorded by Stevens and Van Es in 1964.[122] It is possible to note the above mentioned splitting in the carbonyl region.

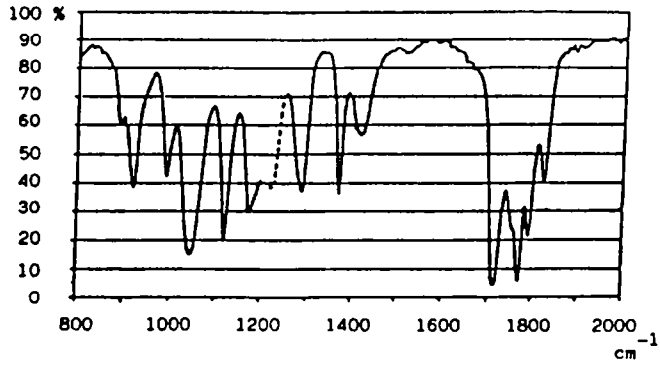


Fig. 3. Infrared spectrum of FAM, equilibrated at 45°C for 1 h (chloroform).[122]

Regarding the pure AFA, prepared from ketene and formic acid, a spectrum of the reaction mixture was recorded in $CHCl_3$:[122] a comparison with the spectra of acetic anhydride, formic acid and acetic acid shows that significant amounts of these compounds are not present in the product. Its bands are consistent with Vledder's spectrum of pure **1**.[145] We report in Fig. 4 a spectrum recorded on a neat distilled sample of AFA,[137] prepared according to Krimen,[80] in the range 200 to 4000 cm^{-1} between KBr windows.

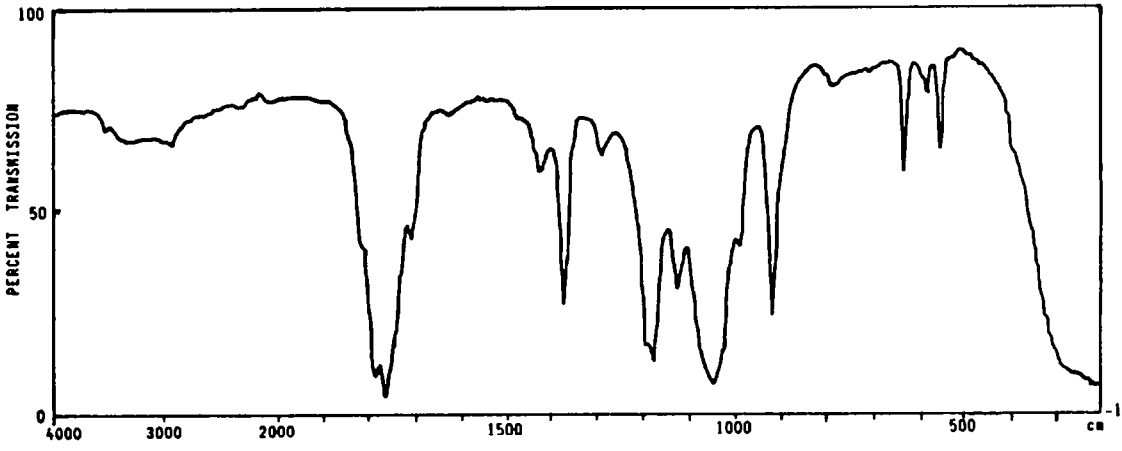


Fig. 4. The infrared spectrum of AFA, neat, through KBr windows.[137]

2.2. *Nuclear magnetic resonance*

^{1}H-NMR measurements were performed by Krimen[80] on **1** (prepared according to his own method) using tetramethylsilane (TMS) as an internal standard; he observed a singlet at $\delta = 5.25$ ppm assigned to the acetyl protons and another singlet at $\delta = 9.05$ ppm assigned to the formyl proton (neat product). When the product was not pure the following extra peaks could be observed: $\delta = 2.05$ ppm ($C\underline{H}_3COOH$), $\delta = 2.20$ ppm [$(C\underline{H}_3CO)_2O$], $\delta = 2.68$ ppm ($C\underline{H}_3COCl$), $\delta = 8.05$ ppm ($\underline{H}COOH$) and $\delta = 8.85$ ppm [$(\underline{H}CO)_2O$]. We report two spectra recorded by Stevens and Van Es:[122] one of FAM, prepared from acetic anhydride and formic acid, and one of AFA, prepared from ketene and formic acid. The former (Fig. 5) confirmed the presence of the mixed anhydride and that of acetic anhydride, formic acid, acetic acid and in addition a peak showed at $\delta = 8.77$

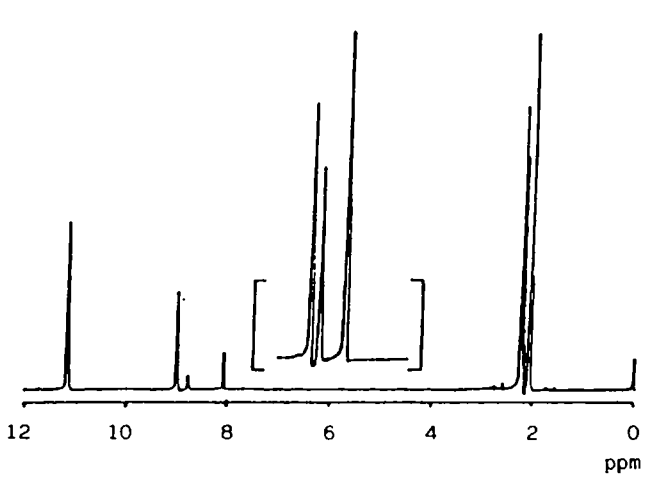


Fig. 5. ^{1}H-NMR spectrum of FAM.[122]

ppm (neat reaction mixture, recorded at regular intervals) that could be assigned to the formic anhydride protons. The latter (recorded on the neat distilled product, Fig. 6) exhibited two peaks the area ratio of which (1 : 3) was in accordance with the structure of **1**. This product seemed to be contaminated only by traces of acetic anhydride and by another substance that was proved to be formic anhydride. Both spectra are consistent with the values of chemical shifts reported by Krimen.[80]

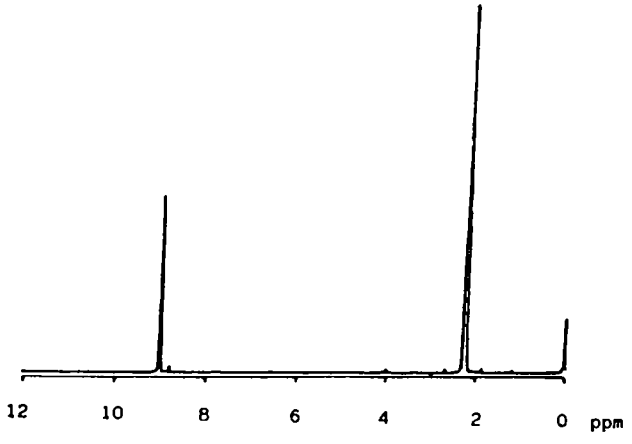


Fig. 6. ^{1}H-NMR spectrum of AFA.[122]

La Palme found two singlets at $\delta = 8.9$ ppm (formyl proton) and at $\delta = 2.2$ ppm (acetyl protons) for **1** prepared by ozonolysis of vinyl acetate.[85] Olah recorded the PMR spectrum of **1** in superacid medium at low temperature (Fig. 1): it showed the deshielded singlet at $\delta = 15.74$ ppm of the [=O—H$^+$] proton and the alkyl protons chemical shifts almost unchanged; a singlet at $\delta = 9.01$ ppm for the formyl proton and the singlet at $\delta = 2.21$ ppm for the acetyl ones.[94] No ^{13}C-NMR studies have appeared in the literature to date. We report the ^{13}C-NMR spectrum of **1** (neat), prepared following Krimen's procedure,[80] showing peaks at 21.07 ($\underline{C}H_3$), 157.92 ($\underline{C}HO$) and 169.27 ($CH_3\underline{C}O$) ppm (Fig. 7) which can be easily distinguished from those of possibly accompanying impurities (CH_3COOH: 20.52, 178.33; Ac_2O: 21.99, 167.48; and HCOOH: 167.09 ppm).[137]

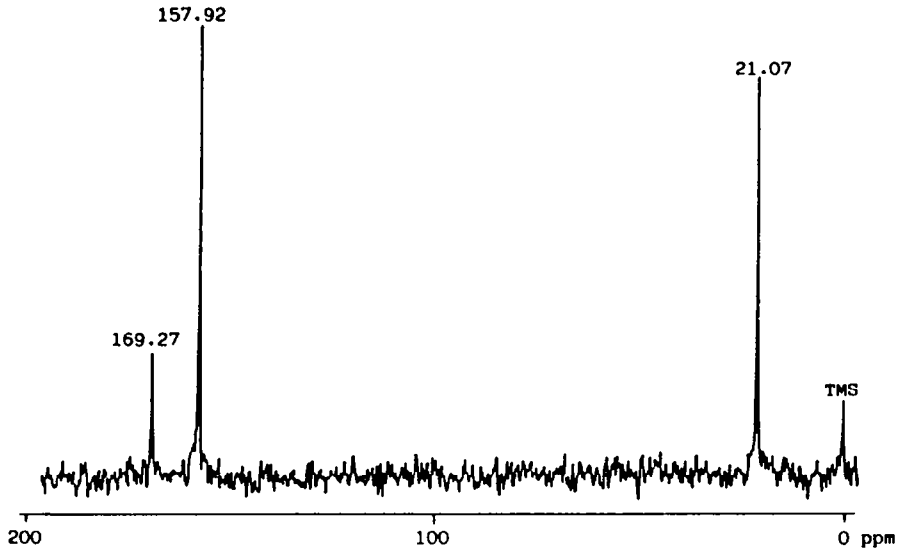


Fig. 7. ^{13}C-NMR spectrum of AFA.[137] Recorded as a neat compound; external standard D_2O, internal standard TMS, on a Bruker WP80 SY spectrometer working at 80 MHz.

2.3. *Other*

No structural microwave, X-ray diffraction, neutron diffraction studies were reported. Similarly, no UV studies have been carried out.

Theoretical studies (SCF–LCAO–MO–INDO calculations) by Curvale indicate a preferential almost planar conformation for **1**.[31] PES and UPS data are not available.

3. KINETIC WORK

The rate of hydrolysis of AFA in acetone–water mixture and its decomposition into acetic acid and carbon monoxide in toluene, were studied by Gold and Jefferson.[55] The hydrolysis in 80% acetone–water was 100 times faster than that of acetic anhydride under the same conditions. In the case of **1** the electronic and steric effects should reinforce each other and therefore **1** should be more reactive with water and with other nucleophiles. The reaction undergoes catalysis by pyridine. The uncatalyzed hydrolysis strictly obeys a first order law.

The decomposition reaction of **1** is catalyzed by amines (pyridine, 2,6-dimethylpyridine, 2- and 4-picoline): it is a first order reaction with respect to **1**. The velocity of this reaction was determined by measuring the rate of evolution of CO from the solution. The order of catalytic efficiency of pyridine and its homologues differs from the order of their basic dissociation constants or from the sequence of their catalytic efficiencies for reactions initiated by a rate determining proton transfer from the substrate to the catalyst. Because of the close similarity of the results for the hydrolysis and the decomposition, the authors suggested that the catalytic action was similar in the two cases and that it consists in an association between the amine and the anhydride molecule. The simplest mechanism in accordance with these observations involves a rate-determining acylium transfer from the anhydride to the base followed by breakdown of the resulting complex as shown below. The second reaction may be the unimolecular decomposition of $[Base–CHO]^+$ or may involve a more complicated sequence. However, the observed reaction order requires that these cannot be kinetically significant. The absence of any detectable formation of CO during the catalyzed hydrolysis of **1** indicates that, in 80% acetone–water, the hydrolysis reaction of the mixed anhydride is much more

rapid than its decomposition.[55] No kinetic work appeared to date in the literature concerning either the rate of formation of **1** under different conditions or the velocity of reactions under catalytic conditions and with different substrates.

$$\underset{\mathbf{1}}{CH_3—CO—O—CHO} + B: \longrightarrow [B—CHO]^+ + AcO^- \longrightarrow BH^+ + CO + AcO^-$$

4. IRRADIATION CHEMISTRY AND MASS SPECTROMETRY

There is no report about the photochemical behaviour of **1**. The mass spectrum of **1** is shown in Fig. 8.

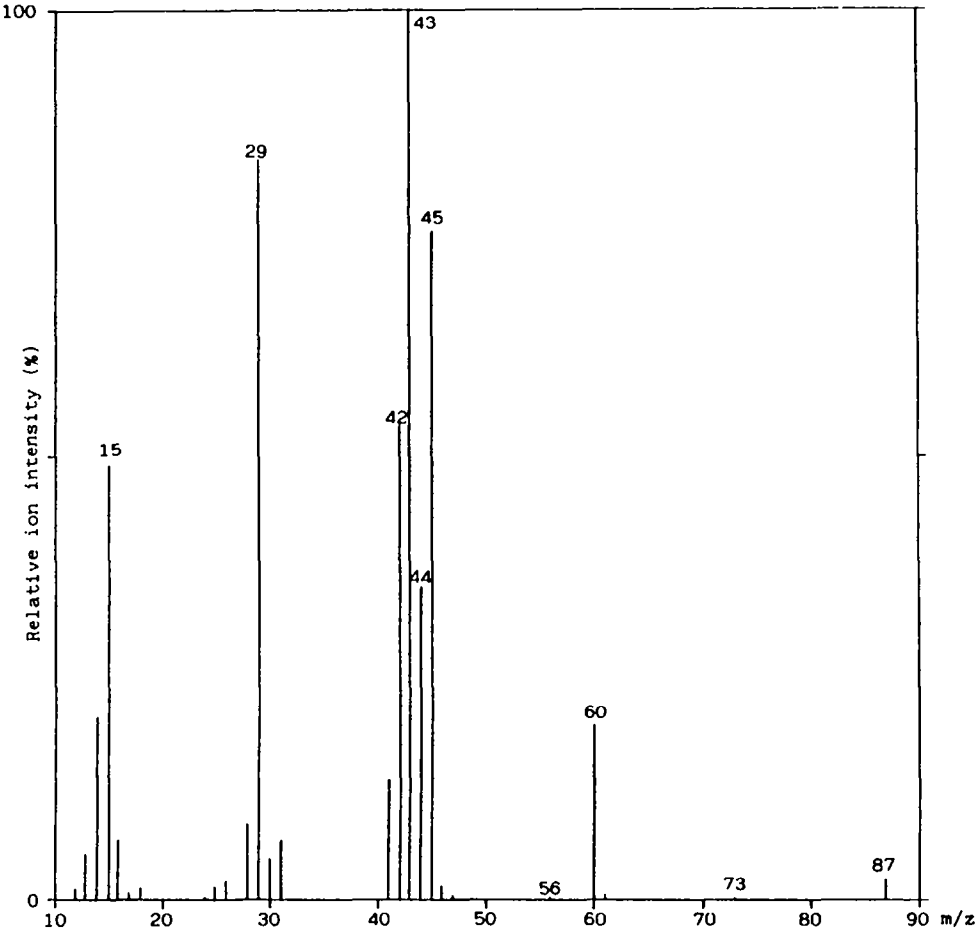


Fig. 8. Mass spectrum of AFA (70 eV).[137]

5. PREPARATIONS

Acetic formic anhydride was synthesized for the first time from anhydrous acetic anhydride and formic acid by Bèhal.[17] This reaction resulted in an equilibrium mixture and the presence of the mixed anhydride in Bèhal's reaction mixture was determined by means of ^{1}H-NMR and IR spectroscopy by Stevens and Van Es.[122] The reaction mixture, obtained by heating the reagents for

one hour at 45°C, contained 75% of **1**, some acetic anhydride and a small percentage of formic anhydride.

Pure **1** has been prepared by the reaction of ethenone (ketene) and formic acid under very mild conditions at room temperature or at low temperature (−80°C).[69,70] Stevens and Van Es found that the yield of this reaction was 70% but the product was contaminated with acetic anhydride. This impurity can indeed be removed by fractional distillation at low pressure. They also found it was necessary to use an excess of ketene because formic acid could not be removed by distillation.[122] Muramatsu[90] obtained a 80–90% yield by this procedure. Similar reactions were examined by Schijf[112] and Krimen:[80] acetyl chloride and sodium formate in an anhydrous solvent at 23–27°C yielded **1** (64% and 75–90%). It is necessary to use dry ether in order to avoid hydrolysis of the mixed anhydride with formation of formic acid (and acetic acid) which catalyzes the decomposition of the product. This procedure produces **1** slightly contaminated with acetic and formic anhydrides. Schijf suggested the use of acid free acetyl chloride and of strictly equimolar amounts of sodium formate in tetrahydrofuran (THF), giving the pure product **1** (60%).[112]

A rapid method of preparing **1** *in situ* was reported by Baltzer.[10] Formic acid, acetyl chloride and triethylamine (TEA) were stirred in THF at −70°C for 10 min.[10] The most recent preparation of pure **1** requires the ozonolysis of vinyl acetate at low temperature (−78°C) in dry dichloromethane with a stream of ozone in oxygen. No data on yields and reaction times were given but the precipitation of the insoluble polymerization product of formaldehyde oxide ($CH_2{=}O^+{-}O^-$) was reported.[85]

The best available synthesis appears to be from ketene and formic acid. This method gives the highest yield and that by Schijf[112] produces the mixed anhydride (60%) with the highest degree of purity (Table 4). The Organic Synthesis preparation by Krimen[80] is completely reliable for synthetic purposes.

Table 4. Summary of the methods to synthesize acetic formic anhydride (**1**)

Reagents	Solvent	Temperature (°C)	Time (h)	Yield (%)	Refs
$HCOOH + (CH_3CO)_2O$	none	[a]	[a]	[b]	48
$HCOOH + (CH_3CO)_2O$	none	50	[b]	[b]	17
$HCOOH + CH_2C{=}O$	HCOOH	[b]	[b]	65	70
$HCOOH + CH_2C{=}O$ (exc)	HCOOH	<10	[b]	70	122
$HCOOH + CH_3COCl + Et_3N$	THF	−70	0.2	[b]	10
$HCOONa + CH_3COCl$	dry ether	23–27	5.5	64	80
$HCOONa + CH_3COCl$[c]	dry THF	0	24.0	60	112
$HCOF + CH_3COONa$	[b]	[b]	[b]	[b]	95
$CH_2{=}CHOCOCH_3 + O_3$	CH_2Cl_2	−78	[b]	[b]	85
$HCOONa + CH_3COCl$	dry ether	27	5.5	91	90
$HCOOH(98\%) + CH_2C{=}O$	ether	[b]	[b]	93	90

[a] Mixing at <50°C, then kept at 4°C during eight days.
[b] Not reported.
[c] Strictly equimolecular amounts.

Krimen's procedure was employed to prepare ^{14}C-formic acetic anhydride from sodium ^{14}C-formate and acetyl chloride[19,89] and ^{13}C-formic acetic anhydride.[45,158,159] Mono, tri and tetra-deuterated compounds ($CH_3COOOCD$, $CD_3COOOCH$ and $CD_3COOOCD$) were prepared from acetyl chloride and DCOONa, CD_3COCl and sodium formate or CD_3COCl and DCOONa, respectively, in diethyl ether at 0°C[145] according to the method of Schijf.[112]

The formation of AFA was observed[59] in the reaction of tartaric dinitrile with lead tetraacetate. The primary reaction product, cyanoformaldehyde, reacted with the acetate ion yielding **1**.

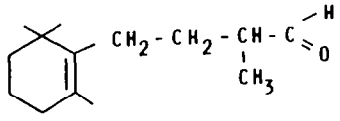
Many authors have prepared the mixed anhydride **1** simply by equilibrating variable amounts of formic acid (usually in large excess) with acetic anhydride. This mixture, which we call Formic acid Acetic anhydride Mixture (FAM, **2**), is used as a formylating agent.

6. CHEMICAL PROPERTIES

The reactions involving AFA and FAM are mostly nucleophilic attacks at the formyl carbon atom by O, N, S, P and C nucleophiles with the generation of the corresponding formate esters, formamides, monothioformates, formyl phosphonates and C-formyl derivatives. There are a few interesting reactions involving organometallic compounds.

6.1. *O-Formylations*

This reaction has been studied extensively on alcohols, phenols, carbohydrates, hydroxy acids and polymeric compounds. Formylation of an aldehyde oxygen (**9**) was reported to give the corresponding enol formate (yield: 3%) in one single configuration.[47]



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6.1.1. *Phenols and alcohols.* Phenols (Table 5) were found to react very slowly with an equivalent of FAM at room temperature. After 10 days, 30% of the phenol had not reacted. After treatment with cold 5% aqueous NaOH followed by fractional distillation, the reaction mixture from phenol and **2** (2 equiv., room temp., 23 days) yielded a product consisting of phenyl formate (92%), phenyl acetate (7%) and unreacted phenol (1%).[124] At higher temperatures (70°C), this reaction loses selectivity yielding formate (40%), acetate (20%) and phenol (40%) after 12 h.[34] Selectivity of

Table 5. Reaction mixture composition (molar percentage) between phenols and a double amount of FAM at room temperature, after 50 days[124]

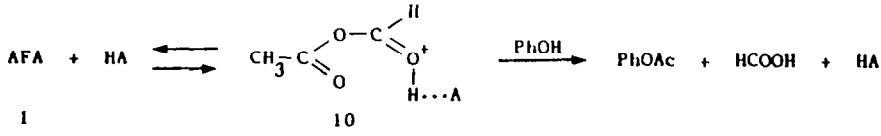
Phenols	Formate (mole %)	Acetate (mole %)	Unreacted phenol (mole %)
Phenol	92	7	1
2-Methylphenol	94	3	3
3-Methylphenol	91	5	4
4-Methylphenol	93	4	3
3,4-Dimethylphenol	94	3	3
2,5-Dimethylphenol	96	2	2
2,6-Dimethylphenol	93	trace	7

this reaction can be improved by carrying out the esterification in a solution of benzene or carbon tetrachloride. This procedure gives the formates (80–85%) containing only negligible amounts of the acetates (< 1%) and unreacted phenols after distillation under reduced pressure (Table 6). In the case of the slowly reacting di-*ortho*substituted phenols (2,6-dimethylphenol) only traces of acetates could be detected in the undistilled formate. Stevens and Van Es also prepared 4-nitrophenyl formate using pyridine and CCl_4 as a mixed solvent. Using **2** they obtained a 70% yield.[124]

Table 6. Formates from phenols and FAM in benzene[124]

Phenols	Reaction time (days)	Yield of distilled formate (%)
Phenol	30	85
2-Methylphenol	60	80
3-Methylphenol	60	80
4-Methylphenol	60	80
3,4-Dimethylphenol	40	85
2,5-Dimethylphenol	60	80
2,6-Dimethylphenol	80	80

Although the esterification with FAM is a good method to prepare pure aryl formates in high yields, it is rather time consuming. Therefore, Stevens and Van Es carried out the esterification with pure AFA, but the formate/acetate ratio obtained (85 : 15) was lower than that (93 : 7) found when using twice the equivalent of **2**. Addition of tertiary bases and sodium formate catalyzed the esterification with both esterifying agents (**2** in slight excess and **1**, 20°C, 24–48 hours) when practically only formate was formed (yield 99%). The procedure is quite general (Table 7) and affords an easy and rapid method of synthesis of pure aryl formates in high yields.[142] A catalysis by 4-methylbenzenesulfonic acid (*p*-toluenesulfonic acid) was noted, but the complete reversion of the reaction outcome was observed: phenyl acetate was the only product of the action of **2** on phenol (yield 99%). The kinetically most active species might be a protonated form of AFA such as **10**.



1 10

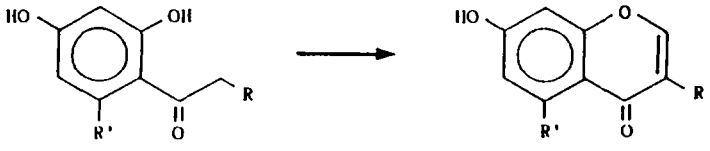
Complications may arise using phenols containing electron withdrawing substituents when their formates fail to crystallize during the esterification. The formate first formed would eventually undergo a transesterification and/or decomposition with acetic acid and/or acetic anhydride. On the other hand a fortunate circumstance is that this kind of aryl formates (Table 7) often crystallized

Table 7. Preparation of aryl formates

By FAM[142]		By AFA[116]		
Aryl group	Yield (%)	Aryl group	Yield (%) no $NaHCO_3$	Yield (%) with $NaHCO_3$
2-*t*-Butyl-4-methylphenyl	83	Phenyl	69	80
6-*t*-Butyl-3-methylphenyl	86	2-Methylphenyl	82	[a]
4-*t*-Butyl-2-methylphenyl	78	3-Methylphenyl	79	[a]
2-Chlorophenyl	77	4-Methylphenyl	73	87
4-Chlorophenyl	74	2-Chlorophenyl	[a]	72
2-Bromophenyl	78	4-Chlorophenyl	[a]	79
4-Bromophenyl	76	2-Isopropylphenyl	65	70
3-Nitrophenyl	79	4-*t*-Butylphenyl	[a]	93
4-Nitrophenyl	82	2,6-Dimethylphenyl	[a]	68
4-Methoxyphenyl	74	4-Acetylphenyl	87	[a]
2,4,6-Trichlorophenyl	80	3-Nitrophenyl	[a]	82
2,4,6-Tribromophenyl	78	4-Nitrophenyl	82	[a]
		3-Methoxycarbonylphenyl	[a]	87
		4-Methoxycarbonylphenyl	[a]	70

[a] Not reported.

from the reaction mixture, thus preventing similar occurrences. Good catalysts for the reaction with electron withdrawing substituents seemed to be 2,6-dimethylpyridine (2,6-lutidine), 2,4,6-trimethylpyridine (2,4,6-collidine) and sodium formate. Another drawback may be due to the decomposition of formate esters to phenols, during work up of the original reaction mixture, by distillation at higher temperatures.[142] Another and faster variation of the original Stevens and Van Es method requires the use of pure AFA (2 eq.) and two equivalents of sodium hydrogen carbonate at room temperature for several hours (Table 7).[120] The insoluble salts were removed by filtration and the solution concentrated under reduced pressure. The pure esters were obtained by fractional distillation *in vacuo* or by recrystallization. α- and β-Naphthols were formylated under these conditions. 2-*t*-Butyl- and 4-methyl-2,6-di-*t*-butyl-phenol did not react because of the steric hindrance whereas 2-nitro-, 2-acetyl- and 2-carbomethoxy-phenol are equally inhibited because their hydroxyl groups are hydrogen bonded to the *ortho*-substituents.[120] In a patent dealing with skin-tanning compositions, 5,6-dihydroxyindole was described to react with AFA in ether (20°C, overnight) to yield both possible O-monoformyl derivatives.[84] Isoflavones **11**, where the substituents R represent several aromatic and heteroaromatic groups, were obtained by cyclization of ketones **12** with **1**, catalyzed by sodium formate or triethylamine, in a high yield reaction, where the initial step is expected to be a regioselective O-formylation.[102] 5,7-Dihydroxyisoflavones **13** with several ring



12 R'=H

11 R'=H

13 R'=OH

substituents were synthesized in quantitative yield .[101] 3-Aryl- or 3-heteroaryl-chromones were obtained by reaction of some α-substituted 2-hydroxyacetophenones with AFA in the presence of a tertiary alkylamine.[76] For other examples of cyclizations: see Section 6.6.

Van Es and Stevens[141] carried out analogous studies on aliphatic alcohols. The esterification of tertiary alcohols by FAM yielded the formate esters exclusively, whereas primary and secondary alcohols produced mixtures containing appreciable amounts of acetate. The velocity of esterification depends upon the alcohol and decreases from primary to tertiary (Tables 8 and 9).[123] The formate

Table 8. Tertiary formate esters from tertiary alcohols and FAM[123]

Formate	Reaction time (h)	Yield* (%)
t-Butyl	48	85
2,2-Dimethylpropyl	48	92
3-Methyl-3-pentyl	168	90
3-Ethyl-3-pentyl	240	94
2-Methyl-2-hexyl	96	90

* No alcohol could be detected in the reaction mixtures after the times indicated; only negligible amounts of acetate (< 1%) were found. The yields refer to distilled products. FAM was used in 50% excess.

may be difficult to purify by distillation due to the presence of the acetate or unreacted alcohol.[141] Temperature changes (10–50°C) affected only the reaction rate. The influence of different molar

Table 9. Esterification of alcohols with FAM (molar ratio 1 : 1.1) at room temperature, by Stevens and Van Es[123]

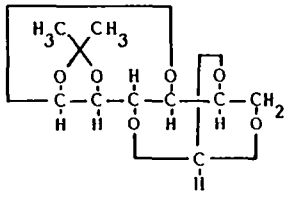
Alcohol	Product ratios: Original reaction mixture formate	acetate	Isolated products formate	acetate
Methyl	82	18	87	13
Ethyl	86	14	92	8
n-Propyl	89	11	87	13
n-Butyl	90	10	90	10
Isobutyl	90	10	90	10
Allyl	87	13	[a]	[a]
Benzyl	97	3	[a]	[a]
Isopropyl	96	4	96	4
sec-Butyl	96	4	96	4
Tertiary alcohols[b]	[a]	[a]	>99	<1

[a] Not reported.

[b] *t*-Butyl (separated yield: 85%), *t*-amyl (92%), 3-methyl-3-pentyl (90%), 3-ethyl-3-pentyl (94%), 3-methyl-2-hexyl (90%).

ratio in order to displace the equilibrium towards mixed anhydride formation led to the exclusive formation of formates in the reactions of 1-propanol and *sec*-butyl alcohol. The most important single influence appeared to be that of the catalyst. Tertiary nitrogen bases and sodium formate increase the selectivity in the esterification of primary and secondary alcohols at 20°C. The reaction is accelerated in the order pyridine > imidazole > sodium formate. The use of acid catalysts (4-methylbenzenesulfonic acid) does not lead to good results yielding considerable amounts of acetate. The authors could not find useful catalysts in the case of tertiary alcohols.[141]

Glucose monoacetonide was dissolved into AFA at 40°C (reaction time: 24 h) to yield the tetracyclic orthoformate **14**. Racemic 1,2,3,4-tetrahydroxybutane slowly dissolved in **1** from which the corresponding tetraformate crystallized out (60%).[48] In the course of the synthesis of the



14

antibiotic A-32390-A, poly-O-formylation of sugar hydroxyl groups by AFA, catalyzed by pyridine[154] was employed. Substrates with the hydroxyl groups masked by acetalization with benzaldehyde were similarly formylated by **1** in formic acid using sulfuric acid as catalyst.

Some nitro-alcohols react smoothly with AFA to yield their formic esters in absolute ether at about 50°C (Table 10).[69] Higher reaction temperatures or addition of sulfuric acid in catalytic amounts caused the transfer of the acetyl moiety to the substrate, as in the case of the reaction with phenols.[124] It can be seen from Table 10 that the yields of formates are not high except in the case of 2-nitro-1-butanol. The presence of the acetate is due to the formation of acetic acid during the esterification procedure and to the consequent equilibrium yielding acetic anhydride.[69] Stevens and Van Es prepared 4-nitrophenyl formate from 4-nitrophenol (1 mole) with a slight excess of FAM (1.5 mole) in presence of pyridine at room temperature. They obtained the formate (70%) after two recrystallizations from carbon tetrachloride.[124]

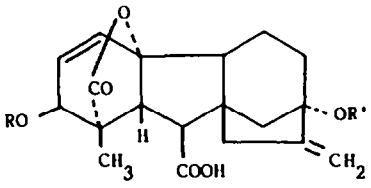
Table 10. Esterification of nitro-alcohols with AFA[69]

Nitro-alcohol	Solvent	Temperature (°C)	Time (min)	Product[a]	Yield (%)
2-Methyl-2-nitro-1-propanol	ether	reflux	480	formate	61
2-Methyl-2-nitro-1-propanol	[b]	50–60	30	formate	44
2-Methyl-2-nitro-1-propanol	[b]	reflux	60	acetate	75–80
2-Methyl-2-nitro-1-propanol	[c]	reflux	60	acetate	75–80
2-Nitro-1-butanol	[d]	[d]	[d]	formate	88
2-Nitro-1-butanol	ether	reflux	480	formate	48
2-Methyl-2-nitro-1,3-propanediol	ether	reflux	480	diformate	53
2-Methyl-2-nitro-1,3-propanediol	[b]	[e]	[e]	diacetate	89

[a] Characterized by conversion to 4-bromophenacyl derivative of the hydrolysis product.
[b] No solvent.
[c] No solvent, one drop of concentrated sulfuric acid added.
[d] Not reported.
[e] Exothermic, instant, vigorous reaction even on cooling with an ice-bath.

In the essential oils technology a procedure for the determination of the free alcohol hydroxy function consisted in the reaction of the mixture under analysis with FAM (72 h, room temperature), acid-base extraction of the reaction mixture and final saponification with 0.5 N alcoholic sodium hydroxide of the separated formates. The free formate anion formed was then titrated suitably.[54,60,86]

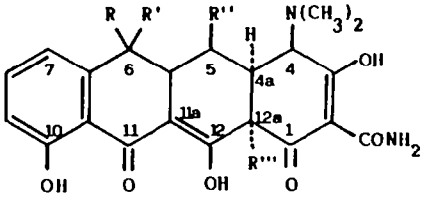
6.1.2. *Hydroxy acids.* Gibberellin A3 (**15**), with AFA (0–2°C, in pyridine, 24 h) yields

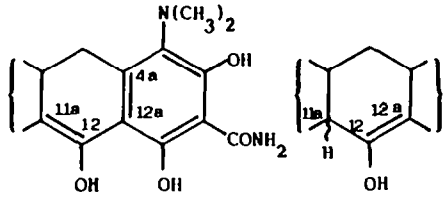


15 R=H, R'=H
16 R=CHO, R'=H
17 R=CHO, R'=CHO

an interesting 3-O-monoformyl derivative (85%, **16**) and O-diformyl compound (13%, **17**).[115] 17-L-Hydroxyoctadecanoic acid was refluxed with FAM in formic acid giving the intermediate formyl derivative which was then transformed into the acid chloride with oxalyl chloride (62%).[135]

6.1.3. *Tetracyclines.* A solution of AFA in acetic acid (acetoformic reagent) reacts with tetracycline **18** in cold pyridine to form O_{12a}-formyltetracycline (**19**, 61%). In boiling toluene the





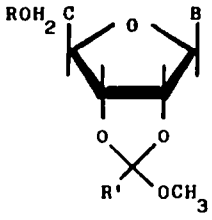
18 R=CH_3, R'=OH, R''=H, R'''=OH
19 R=CH_3, R'=OH, R''=H, R'''=OCHO
22 R=H, R'=H, R''=H, R'''=OH
23 R=H, R'=H, R''=H, R'''=OCHO
24 R=CH_3, R'=OH, R''=OH, R'''=OH

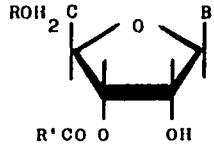
20 21

formate **19** is transformed into 4*a*,12*a*-anhydrotetracycline (**20**) by pyrolytic *cis*-elimination of formic acid. **19** Also undergoes catalytic hydrogenolysis giving 12*a*-deoxytetracycline (**21**, 42%).

6-Demethyl-6-deoxytetracycline (**22**) similarly produces O_{12a}-formyl-6-demethyl-6-deoxytetracycline (**23**). 5-Hydroxytetracycline (**24**) undergoes a more complex reaction with AFA in pyridine producing a diformate of undetermined structure.[22]

6.1.4. *Ribonucleosides.* Reaction of the appropriate anhydride and methoxyalkylidene derivatives of ribonucleosides (**25**) in the synthesis of oligoribonucleotides by the phosphotriester approach afforded the 5′-O-acyl-2′,3′-methoxyalkylidene derivative **26** which was then submitted to acidic hydrolysis to regenerate the 2′- and 3′-hydroxy groups. FAM and 2′,3′-benzylideneuridine (**27**) yielded 3′-O-benzoyl-5′-O-formyluridine (**28**) after acidic hydrolysis,[49] whereas the product of reaction between 2′,3′-O-methoxymethylideneuridine (**29**) and **2** was the diformyl derivative 3′,5′-di-O-





25 R=H; **26** R=acyl

28 R=HCO, R'=Ph, B=uracil

27 R=H, R'=Ph, B=uracil

30 R=HCO, R'=H, B=uracil

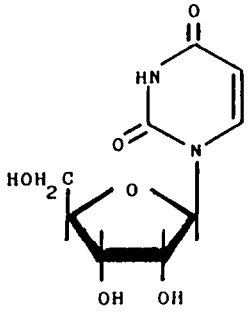
29 R=H, R'=H, B=uracil

31 R=H, $R'=CH_3OCH_2$,

32 R=HCO, $R'=CH_3OCH_2$,

a B=uracil
b B=6-N-(4-methoxybenzoyl)adenine
c B=2-N-benzoylguanine

formyluridine (**30**) (68%).[58] 2′,3′-O-(Dimethoxyethylidene)uridine (**31a**), 6-N-(4-methoxybenzoyl)-2′,3′-O-(dimethoxyethylidene)adenosine (**31b**) and 2-N-benzoyl-2′,3′-O-(dimethyoxyethylidene)-guanosine (**31c**) were treated with **2** at low temperature in pyridine to give, after treatment with 95% formic acid, the corresponding 5′-O-formyl-3′-O-(methoxyacetyl) derivatives **32a** (44%), **32b** (60%) and **32c** (77%).[104] The selective sensitivity of formate esters towards methanolysis in comparison with acetates made formylation with AFA a method of choice for the protection of the hydroxyl functionalities of the sugar moiety of some nucleosides such as uridine (**33**), 6-azauridine



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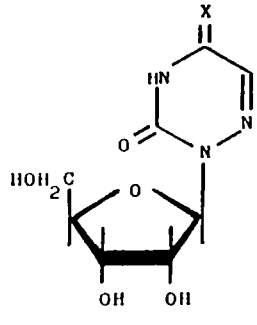


34 X=O

35 X=NH

(**34**) and 6-azacytidine (**35**). Poly-O-formylation occurred when there were free hydroxyl groups. No N-formyl derivative was isolated after attempted formylation of 6-azacytidine.[160]

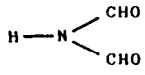
6.1.5. *Hydroxy polymeric systems.* FAM has also been used in the preparation of formyl derivatives of hydroxy polymeric systems. Poly(4-formyloxy)ethenylbenzene (poly-*p*-formyloxystyrene) can be obtained by either of two different routes: polymerization of 4-formyloxyethenylbenzene monomer or by chemical modification of poly(4-hydroxy)ethenylbenzene chain. Both of these routes involve the formylation of a phenolic substrate by **2**. The latter route is somewhat slower than the corresponding formylation of the lower molecular weight compound. 4-Methylphenol (*p*-cresol) gave *p*-tolyl formate (70%).[131]

6.1.6. *N-Oxides.* The peculiarity of the formyl group circumvents the Polonovski reaction[103] and other rearrangements[75,105] to produce clean and quantitative deoxygenations of N-oxides of tertiary

amines using AFA, via the assumed intermediacy of O-formyl derivatives. Sulfoxides were found to be unreactive toward **1**.[132]

6.2. *N-Formylations*

6.2.1. *Amines and polyamines.* Ammonia in dry ether reacted with AFA at 0°C yielding the corresponding formamide. No mention was made of any polyformylation products such as the diformamide (**36**) or triformamide (**37**), which are known compounds.[5,6,121]



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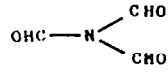

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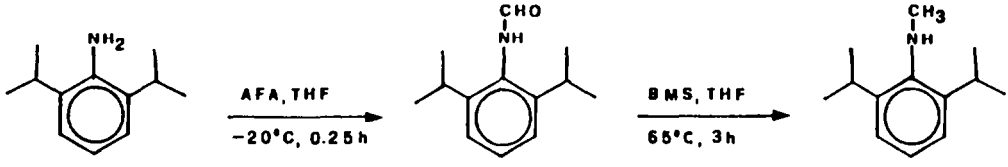
An efficient and general one pot procedure for the N-monomethylation of primary amines calls for the formylation of the amino group with excess FAM under mild conditions.[81] The yields are excellent even for weakly basic and sterically hindered aromatic amines, like 4-nitrobenzeneamine,



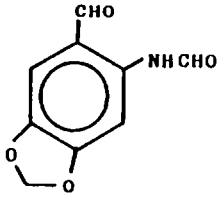
4-amino-3-chloro-N,N-dimethylbenzenesulfonamide and 2,6-diisopropylbenzeneamine (Table 11). N-Diformylation was not observed, a fact which is important when the formamides are to be reduced to N-methylamines.[81] *n*-Octadecylamine gave only N-monoformylation at 0°C in pentane–ether, whereas some 10% N,N-diformylation product was obtained when **2** was used without solvent under reflux.[14]

N-Formylation by FAM forms the basis of an analytical method for tertiary amines in presence of primary and secondary amines.[56]

A large number of N-formylations have been reported on aliphatic and aromatic amines. 2-Amino-4,5-methylenedioxybenzaldehyde was N-formylated to **38** with AFA in dichloromethane (1 h, room temp., 62% yield).[11] FAM was successfully used (1 h, 60°C) in N-formylating 2-(methylamino)benzaldehyde (**39**, 40%) and its 2,4-dinitrophenylhydrazone to give **40** (92%).[41] The heterocyclic compound **41** (R=H) was formylated with AFA in the patented preparation of the

Table 11. Formylation of primary amines by FAM according to Krishnamurthy[81]

Primary amine	Temperature (°C)	Time (h)	Yield (%)
Benzeneamine	−20	0.25	100
2,6-Dimethylbenzeneamine	−20	0.25	100
2,6-Diisopropylbenzeneamine	−20	0.25	99
2-Aminophenol	−20	0.25	100
4-Methylbenzeneamine	−20	0.25	99
4-Bromobenzeneamine	−20	0.25	99
4-Iodobenzeneamine	−20	0.25	100
2,4-Dichlorobenzeneamine	−20	0.25	100
4-Nitrobenzeneamine	0	0.25	100
2-Chloro-4-nitrobenzeneamine	25	3.00	100
Ethyl 4-aminobenzoate	−20	0.25	97
4-Amino-3-chloro-N,N-dimethylbenzenesulfonamide	25	2.00	99
Benzylamine	−20	0.25	99
3-Aminopyridine	−20	0.25	99



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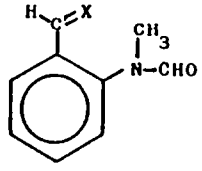
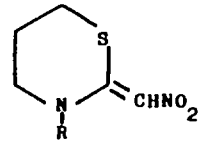


39 X=O

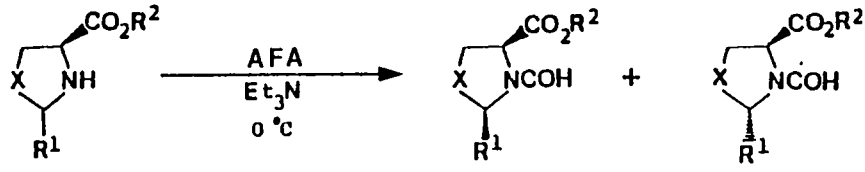
40 X=N-NH-(2,4-dinitrophenyl)



41 R=H

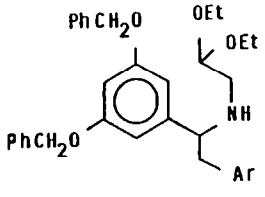
42 R=CHO

N-formyl derivative **42** (R=CHO), an insecticide.[64] A number of N-unsubstituted oxazolidines and thiazolidines (**43**, X=O or S) were N-formylated in excellent yields with **1**: the stereochemical selectivity was found to be about 3 : 1 (*cis*, **44**/*trans*, **45**).[7]



43 X = O,S 44 45

Configuration was preserved when one enantiomer of 1-phenylethylamine was formylated by FAM.[130] **2** in the presence of sodium acetate gave a quantitative yield of the N-formyl derivative by reaction with N-[α-(3,5-dibenzyloxyphenyl)-β-(3,4,5-trimethoxyphenyl)]ethylaminoacetaldehyde diethylacetal (**46**) at room temperature.[155] The steroidal amine 3α-amino-(25*R*)-5α-spirost-9(11)-



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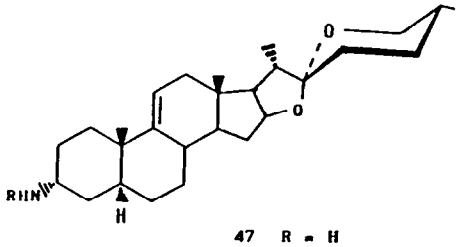
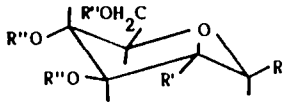
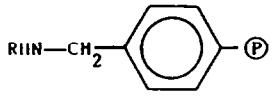


47 R = H

48 R = CHO

ene (**47**) was formylated to **48** with AFA.[14] 2-Deoxy-2-amino-β-D-glucose 1,3,4,6-tetraacetate (**49a**) was N-formylated to **49b** (94%).[14] The formylation of 2,3,4,6-tetra-O-benzoyl-β-D-glucopyranosylamine (**50a**) by **1** at room temperature (6 h) in ethyl acetate yielded the corresponding N-formyl derivative **50b** quantitatively.[91] Both (±)- and *meso*-1,2-diamino-1,2-diphenylethane were





49a R=OAc, R'=NH_2, R"=Ac

49b R=OAc, R'=NHCHO, R"=Ac

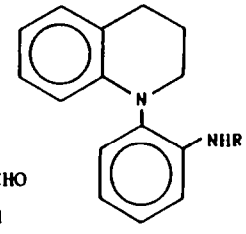
50a R=NH_2, R'=OOCPh, R"=COPh

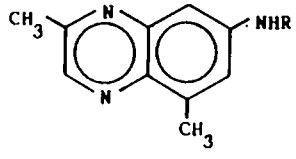
50b R=NHCHO, R'=OOCPh, R"=COPh

51 R=H

52 R=CHO

bis N-formylated by **1** in 60% yield.[14] AFA was also successfully used in the N-performylation of aminomethyl-polystyrene (**51**) to **52** in dichloromethane in the course of the synthesis of isocyanomethyl-polystyrene resins. The reaction was performed at room temperature for 72 h with quantitative yields.[119] The weakly basic 2-aminobenzonitrile was formylated by FAM (0.16 h, 60°C, 77%).[71] Analogously, 2,6-dichloro-4-nitroaniline was formylated (64%) with **2**.[140] A very bulky group in *o*-position did not exclude the formation of the formamide **53** (98%).[53] The aromatic amine **55** gave its N-formamide (**56**) with AFA.[92]





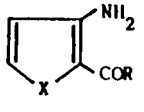
53 R=CHO

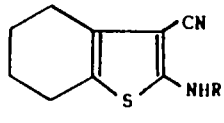
54 R=H

55 R=H

56 R=CHO

An extensive literature exists for heterocyclic compounds. Side chain N-formylations and ring N-formylations have been reported. 2-Amino-3-picoline reacted with FAM giving N-formylpicoline (82%).[29] 3-Aminothiophene, 3-benzylaminothiophene, 3-methylaminothiophene, 3,4-diaminothiophene and 3,4-di(benzylamino)thiophene were N-formylated by **2** in excellent yields.[97] 2-Acyl-3-amino-thiophenes and -selenophenes (**57**) were N-formylated with AFA,[3] whereas a ring substituted 2-thienylamine (**58**) could be N-formylated to **59** (83%) by FAM.[71]





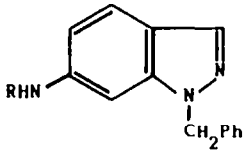
57

X=S, Se; R=H, CH_3

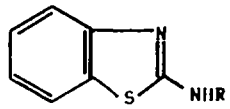
58 R=H

59 R=CHO

1-Benzyl-6-aminoindazole (**60**) in DMF was formylated by AFA producing the 6-formamido derivative (**61**).[61] 2-Aminobenzothiazole (**62**) in anhydrous ether was formylated by **1** giving **63** (70%).[28]

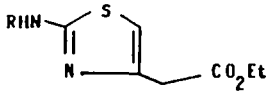


60 R=H
61 R=CHO

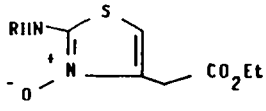


62 R=H
63 R=CHO

An uncommon instance of either formylation or acetylation which depends upon the substrate is shown by a 2-aminothiazole derivative and its N-oxide. When exposed to an excess of FAM, 2-amino-4-ethoxycarbonylmethylthiazole (**64**) undergoes formylation producing the N-formyl derivative **65** (91%) whereas the corresponding N-oxide **66** in dry chloroform at $-10°C$ yields the

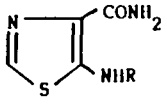


64 R=H
65 R=CHO

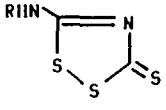


66 R=H
67 R=Ac

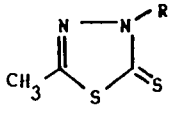
N-acetyl derivative **67** (65%) exclusively.[99] FAM (83°C, 4 h) reacted with 5-aminothiazole-4-carboxamide (**68**) to yield the corresponding 5-formamido derivative (**69**, 95%).[129] In the absence of solvent the reaction between 5-amino-1,2,4-dithiazole-3-thione (**70**) and AFA gave 5-N-formyl-



68 R=H
69 R=CHO



70 R=H
71 R=CHO
72 R=Ac



73 R=H
74 R=CHO

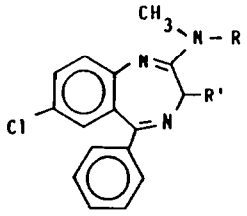
amino-1,2,4-dithiazole-3-thione (**71**, 85%). In pyridine this reaction yielded a mixture of the 5-N-acetyl (**72**, 80%) and the 5-N-formyl (**71**, 6%) derivatives.[153]

2-Methyl-1,3,4-thiadiazolin-5-thione (**73**) was formylated by FAM to yield **74** (75%).[156] **2** In excess was used in the formylation of a number of heterocyclic amines (Table 12).[68]

Table 12. Formylation of heterocyclic amines with FAM at room temperature[68]

Amine	Product	Yield (%)
2-Aminoquinoxaline	2-Quinoxalinoformamide	91
2-Aminothiazole	2-Thiazolylformamide	64
2-Amino-5-nitrothiazole	2-(5-Nitrothiazolyl)formamide	84
2-Aminobenzimidazole	2-Benzimidazolylformamide	83
2-Aminobenzothiazole	2-Benzothiazolylformamide	94

N-(7-Chloro-5-phenyl-3H-1,4-benzodiazepin-2-yl)-N-methylhydroxylamine (**75**) incorporates both acyl residues of FAM (16 h, room temp., 32% yield) at two different sites yielding the N-formyl-3-acetyl derivative **76** (32%). The sites of acylation were confirmed by performing the reaction on 3-acetoxy-7-chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine (**77**) which pro-

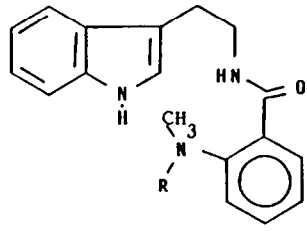


75 R=OH, R'=H

76 R=CHO, R'=OAc

77 R=H, R'=OAc

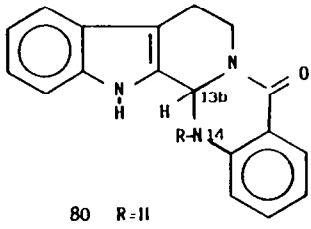
78 R=CHO, R'=OAc



79 R=H

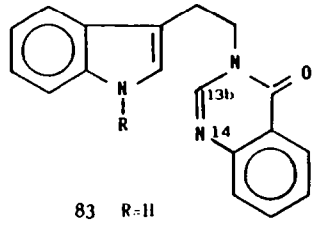
81 R=CHO

duced the N-formyl derivative **78**.[109] N-(2-Methylaminobenzoyl)tryptamine (**79**) yielded N-[2-formyl-N-methylamino)benzoyl]tryptamine (**81**, 85%) and 13*b*,14-dihydrorutaecarpine (**80**) yielded 14-formyl-13*b*,14-dihydrorutaecarpine (**82**, 96%) when treated with AFA at room temperature. The product **83** undergoes ring closure followed by N-formylation giving **82** (76%), by treatment with



80 R=H

82 R=CHO

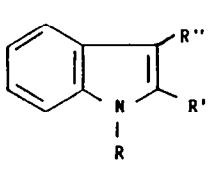


83 R=H

84 R=CHO

1 at 25–60°C. It can be seen that the less basic heteroaromatic nitrogen is prevented from being formylated, although traces of the ring formylated derivative **84** could be detected.[21]

Some indole derivatives (**85**, **86**, **87** and **88**) were treated with AFA or FAM, in the dark. C-Formylation in the 3-position occurred, whenever this position was free (**85**, **86** and **87**), but the primary reaction product then condensed with the original substrate yielding products of the type



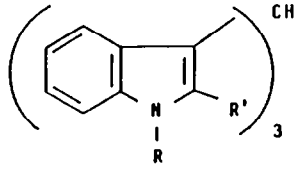
85 R=H, R'=H, R''=H

86 R=CH_3, R'=H, R''=H

87 R=H, R'=CH_3, R''=H

88 R=H, R'=H, R''=CH_3

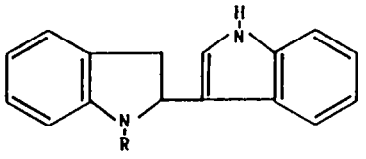
96 R=CHO, R'=H, R''=CH_3



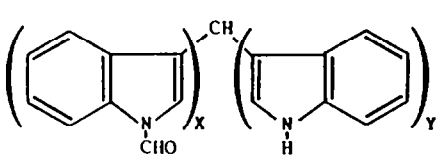
89 R=H, R'=H

90 R=CH_3, R'=H

91 R=H, R'=CH_3



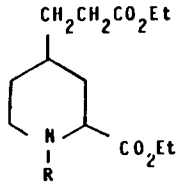
92 R=CHO
93 R=H



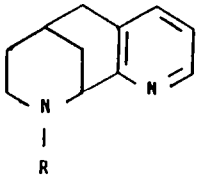
94 X=1, Y=2
95 X=2, Y=1

89, **90** and **91**. In the case of indole (**85**) dimerization and N-formylation gave **92**. Product **92** was also obtained by direct N-formylation with **1** of 2-(3-indolyl)indoline (**93**, 80%). If this reaction is performed at higher temperature (50°C), products of mono- and di-N-formylation of **89** (**94** and **95**) were also observed. 3-Methylindole (**88**) underwent N-formylation giving **96** (28%).[20]

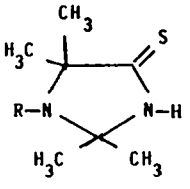
Ethyl 2-ethoxycarbonyl-4-piperidinepropionate (**97**) in ether was formylated giving ethyl 2-ethoxycarbonyl-1-formyl-4-piperidinepropionate (**98**, 79%) by FAM. The bicyclic amine **99** (2-benzoyl-1,2,3,4,5,6-hexahydro-1,5-methanopyrido[2,3-*c*]azocine) gave the N-formyl derivative **100**



97 R=H
98 R=CHO

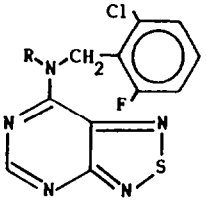


99 R=H
100 R=CHO

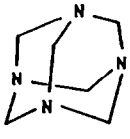


101 R=H
102 R=CHO

(58%).[1] 4-(Diphenylmethyl)piperidine was formylated by **2** at 25°C producing 1-formyl-4-(diphenylmethyl)piperidine (71%).[114] Formylation of piperidine-4-carboxylic acid was successfully achieved (76%) by **2** without any solvent.[125] This experiment shows that a free carboxyl function does not interfere with the N-formylation reaction. A regiospecific formylation by FAM took place with 2,2,5,5-tetramethyl-4-thioxoimidazoline (**101**) leading to 1-formyl-2,2,5,5-tetramethyl-4-thioxoimidazoline (**102**, 86%).[27] 7-(2-Chloro-6-fluorobenzyl)amino[1,2,5]thiadiazolo[3,4-*d*]-pyrimidine (**103**) reacted with **2** yielding its 7-N-formyl derivative (**104**, 91%).[65]



103 R=H
104 R=CHO



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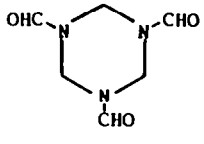
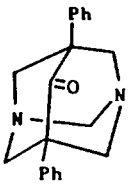


106

The tetracyclic structure of hexamethylenetetramine (**105**) was cleaved by FAM yielding the compound **106** (68%).[51] Similar behaviour was exhibited with AFA by diazamantanone **107** yielding the N,N'-diformyldiazabicyclononanone **108** (42%). Nitrotriazaadamantane **109** gave the nitrotriazabicyclononanes **110** and **111**.[2]



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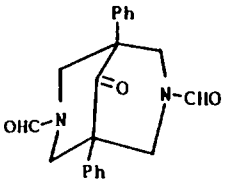

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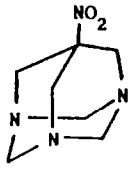

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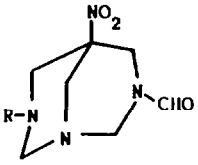
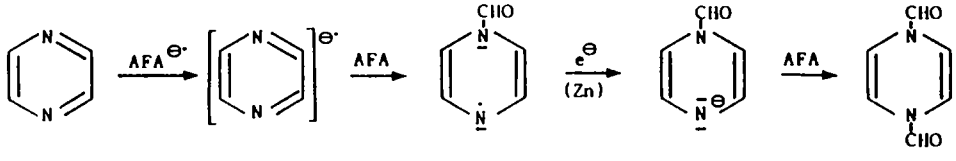


110 R=CHO

111 R=Ac

2-Furylamines were N-formylated with FAM (60°C, 0.5 h, 58–71%) and this was followed by subsequent reactions of the initial formamides.[71] Reaction of some 2-aminopyrroles gave the corresponding formamides, which might react further giving cyclic products.[71]

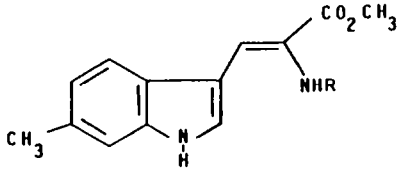
Reductive 1,4-diformylation of pyrazine (**112**) to 1,4-diformyl-1,4-dihydropyrazine (**113**, 28%) was accomplished by the combined use of AFA and zinc powder. The mechanism of the reaction was shown to be rather peculiar and different from the electrochemical reduction–diacylation of **112**. Zinc metal reacts first with **1** yielding the corresponding radical anion (not directly observed), which eventually transfers one electron to pyrazine. The newly formed radical anion (**114**) then reacts with **1** to yield 1-formyl-1,4-dihydropyrazin-4-yl radical (**115**), which will be reduced to the corresponding anion **116** by zinc and finally formylated to the final product **113**.[57]



112 114 115 116 113

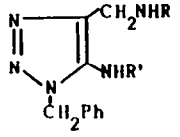
Formylation of all the amino groups took place in the reaction between AFA and some polyamines. *cis,cis*-1,3,5-Triaminocyclohexane,[87] 1,2-bis(2-aminophenoxy)ethane and 1,2-bis(2-amino-4-*tert*-butylphenoxy)ethane[8] yielded the corresponding N-performylated derivatives respectively in 65%, 99% and 87% yield.

As it was suggested from the reactions described above of some amino derivatives of indole compounds, the heterocyclic nitrogen is much less reactive to formylation. The amino group of methyl (*Z*)-α-amino-6-methylindole-3-acrylate (**117**) was exclusively formylated by **1** to **118** (82%)



117 R=H

118 R=CHO



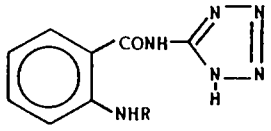
119 R=H, R'=H

120 R=CHO, R'=H

121 R=CHO, R'=CHO

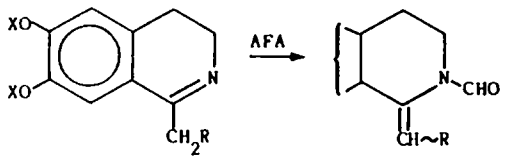
at room temperature in tetrahydrofuran.[66] Selective formylation at the strongest basic centre of 4-amino-5-aminomethyl-3-benzyl-1,2,3-triazole (**119**) was observed affording 4-amino-3-benzyl-5-formamidomethyl-1,2,3-triazole (**120**, 80%) with an excess of AFA in dry pyridine at 22°C. The same compound exhibited different behaviour yielding the diformyl derivative 3-benzyl-4-formamido-5-

formamidomethyl-1,2,3-triazole (**121**, 60%) when added to **1** at 20°C.[4] The last step in the patented preparation[98] of an antiallergic drug is the formylation of 5-anthranoylaminotetrazole (**122**) with **1** giving **123**. Three 6,7-disubstituted 1-alkyl-3,4-dihydroisoquinolines **124** reacted in their tautomeric form (enamine) with **1** to yield Z and E formamides **125**.[9] Another instance of imine–enamine



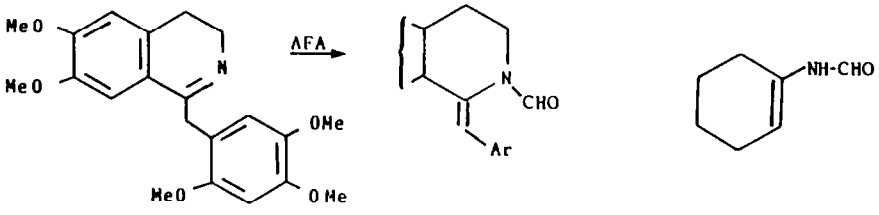
122 R=H

123 R=CHO



124 R=H, CH_3 125

isomerisation under the conditions of N-formylation by AFA is given by the preparation of the enamide **126** (99%) from the 3,4-dihydro-6,7-dimethoxy-1-(2,4,5-trimethoxybenzyl)isoquinoline (**127**).[62] In the one pot reaction of ketoximes with titanium(IV) acetate and **1** in DMF, the final outcome is the interception of the corresponding N-formylenamine **128**, which is stable in two



127 126 128 (E- and Z-)

rotameric forms under these conditions. Nine successful examples of this reaction were offered with yields from good to excellent.[13]

The first synthesis of a stable salt of the type $HCOX^+Y^-$, where X is an onium ligand, was recently reported. The reaction product between a trimethylsilyl halide or trifluoroacetate and 4-dimethylaminopyridine was put to react with AFA to yield (70–90%) N-formyl-4-dimethylaminopyridinium salts.[151] Traces of the pyridine caused *rapid* decarbonylation whereas the ion only slowly decomposed to CO under the same conditions. This points to a dual mechanism for the reaction.

6.2.2. *Amino acids.* Amino acids of widely different nature have been N-formylated either with AFA or FAM. N-Formylation of amino acids has been achieved using **2** in good yield, without racemization of the parent amino acids. However, this procedure has the drawback that an excess of reagents (acetic anhydride and formic acid) is necessary because the real formylating agent seems to be the mixed anhydride and its concentration is determined by the equilibrium constant.[50,117,149] Muramatsu therefore suggested the use of pure **1** in the formylation and this method required only a two or three molar excess of formylating agent.[90] Even when acetic acid was used as the solvent, formylation occurred and acetylation did not. Amino acids, as well as the alanine ethyl ester, were formylated by this method with retention of configuration in good yields (70–90%, see Table 13).[90]

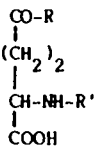
The N-formylation of glutamic acid (**129**) was performed by several authors.[25,37,90,127] The procedure described by Borek and Waelsch for L-glutamic acid gave 72% yield. In the same paper there is the analogue preparation of N^{α}-formyl-L-glutamine (**130**, 62%) and of N-formyl-L-glutamic acid 5-benzyl ester (**131**, 80%).[25] Glycine was quickly formylated by AFA at 0°C (1 min, 94% yield).[126] Racemic 6-chlorotryptophan (**132**) was formylated by **1** in tetrahydrofuran to **133** (100%

Table 13. Formylation of amino acids with AFA in excess[90]

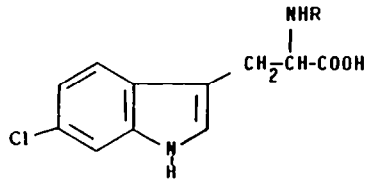
Amino acid	Time (min)	Solvent	Yield (%)	Molar excess of **1** (%)
Glycine	120	formic acid	85	200
Glycine	120	acetic acid	76	200
Glycine[126]	1	no solvent	94	254
DL-Alanine	[a]	formic acid	94	200
L-Valine	[a]	formic acid	84	277
L-Leucine	[a]	formic acid	70	200
L-Methionine	[a]	formic acid	77	200
L-Phenylalanine	[a]	formic acid	83	88
L-Tyrosine	120	formic acid	84	200
L-Glutamic acid	[a]	formic acid	35[b]	27
β-Alanine	[a]	formic acid	79	271
DL-Alanine ethyl ester	180	formic acid	85	93
L-Alanine methyl ester[73]	180	chloroform	73	0[c]
DL-[^{15}N]Alanine methyl ester[147]	[d]	chloroform	[a]	9

[a] Not reported.
[b] Better yields are reported in literature by the usual FAM method.[37,127]
[c] With equimolecular amount of triethylamine.
[d] Overnight.

yield, 20 min at 20°C).[100] Amino acids containing hydroxyl groups such as tyrosine (yield not reported)[149] and 3,4-diacetyloxyphenylalanine (86%)[23] under mild conditions were formylated by FAM. Basic amino acids required a special procedure for the selective formylation of one of the two amino groups: however this method did not use **2**.[93] In two other reports D- or L-lysine hydrochloride was treated with FAM or AFA to yield the n$^{\alpha}$-formyl derivative. The regioselectivity is remarkable. Sodium salts of carboxylic acids function as catalysts (yields: 92%).[107,108]



129 R=OH, R'=H
130 R=NH_2, R'=CHO
131 R=OCH_2Ph, R'=CHO

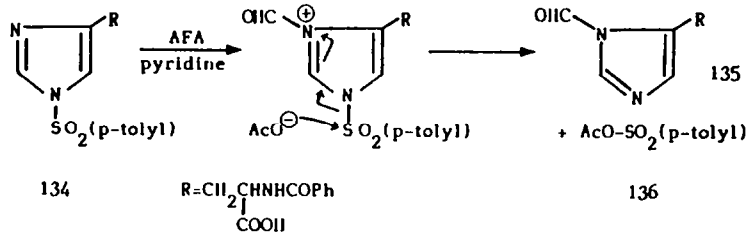


132 R=H
133 R=CHO

Amino acids were N-formylated using a large excess of FAM at 0°C, then at 50°C during 15 min under argon at 4°C. N-Formylleucine was prepared (60%),[150] DL-cystine was N,N'-diformylated by a modified procedure (55%,[36] 69%[50]) which amounts to the *in situ* formation of formic acetic anhydride: the product was recrystallized from water without undergoing hydrolysis.[36] An improved procedure (87%) used treatment of cystine only with formic acid. Treatment of DL-N,N'-diformylcystine with Zn and formic acid afforded DL-N-formylcysteine (40%).[50]

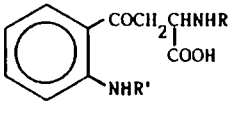
N-Formylhydroxyaminoacetic acid (hadacidin) was obtained from hydroxyaminoacetic acid and FAM at room temperature (no yields are reported).[72] In a different context another hydroxylamine, namely 4-(4'-chlorophenoxy)phenylhydroxylamine, was formylated with **2**.[83]

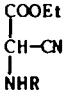
The N^{Im}-tosyl group could be quantitatively removed from N$^{\alpha}$-benzoyl-L-hystidine (**134**) with AFA and a catalytic amount of pyridine in 3 h to give **135**. This reaction is believed to involve the



formylation of the other ring nitrogen and the subsequent elimination of acetic tosyl anhydride (**136**).[138] The formyl group has been used extensively as a blocking group in the synthesis of peptides.[117,149] The formyl protective group can be selectively removed without cleavage of peptide linkages by acid hydrolysis with a slight excess of 0.5 N hydrochloric acid in methanol either at room temperature for 48 h or by refluxing for 1 h.[117] These peptides retain a high optical purity (85–90%) because the formyl group can be introduced without racemization of the parent amino acid. The N-formyl group is relatively stable towards basic hydrolysis. Saponification of esters of amino acids in aqueous dioxane gave the corresponding N-formylamino acids in yields consistently better than 85%. This provides a choice between extending the peptide chain either at the amino or at the carboxyl ends.

The acylation of kynurenine (**137**), a compound formally exhibiting an aliphatic and an aromatic primary amino group, using FAM showed a peculiar dependence upon reaction conditions and the molar ratio $HCOOH/Ac_2O$. When an equimolecular amount of reagents was used and acetic anhydride was added to a solution of **137** in formic acid the selective acetylation of the aromatic amino group (**138**) occurred without affecting the aliphatic group. In contrast using twice the amount of acetic anhydride then diacylation occurred and the resulting product contained one acetyl and one formyl group (**139**). The aromatic amino group was acetylated whereas the aliphatic group was formylated.[32] Formylation of phenacylglycine, (2-nitrophenacyl)glycine, tryptophan and phenacylalanine did occur under the same conditions ($HCOOH/Ac_2O$ 1:1), whereas 2-aminobenzoic acid underwent mainly acetylation. N-Acetylation in the above reactions was rationalized as being due to a more rapid reaction of acetic anhydride with the aromatic amino groups than with formic acid. If acetic formic anhydride is allowed to form, by adding the substrate to the reaction mixture after a long enough period, then only formylation occurred. Using these modified conditions N′-formyl-DL-kynurenine (**140**, 90%) was obtained. Further additions of FAM gave the N,N′-diformyl-kynurenine (**141**).[32] Low yields of ethyl 2-cyano-2-formamidoacetate (**142**, 38%) were obtained by

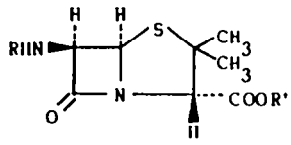


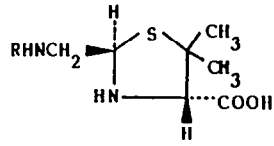


137 R=H, R'=H **140** R=H, R'=CHO **142** R=CHO
138 R=H, R'=Ac **141** R=CHO, R'=CHO **143** R=H
139 R=CHO, R'=Ac

the formylation of ethyl 2-amino-2-cyanoacetate (**143**) by AFA.[67] Some α-aminomethyl esters were N-formylated in $CHCl_3$ with triethylamine and a stoichiometric amount of **1** (3 h, room temp.). Typically, alanine methyl ester was formylated (93%).[73]

Formylation of penicillins by **1** has been achieved. All the following substituted penicillanic (**144** and **145**) and penilloic acids (**146**) gave products of N-formylation from low (−70°C) temperature reactions: sodium (6*R*)-6-formamidopenicillanate (**147**), benzyl (6*S*)-6-formamidopenicillanate





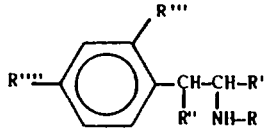
144 R=H, R'=Si(CH$_3$)$_3$ 147 R=CHO, R'=Na 146 R=H

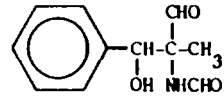
145 R=H, R'= CH$_2$Ph 148 R=CHO, R'= CH$_2$Ph 149 R=CHO

(**148**, 71%) and (2*R*,4*S*)-5,5-dimethyl-2-formamidomethylthiazolidine-4-carboxylic acid (**149**, 40%).[10]

6.2.3. *Amino alcohols and amino phenols.* The amino group is usually by far more reactive than the hydroxyl group towards anhydrides. It is therefore usually possible to obtain the formamide from an amino alcohol.

A comparative study of the N-formylation of some sympathomimetic amines, **150**, **151**, **152**, **153**, **154** and **155** (hydroxyamines), using formic acid, formamide and FAM was accomplished. Complex mixtures were obtained in all cases, but the N-formyl derivatives could be separated.[144] The results are said to be best in the case of **2**. **151** Apparently gave the N,C$^{\alpha}$-diformyl derivative **156** on the basis of weak evidences. This requires confirmation.

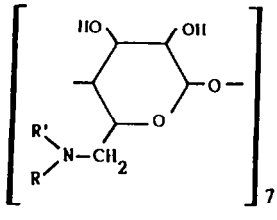




	150	151	152	153	154	155
R	CH$_3$	H	CH$_3$	CH(CH$_3$)$_2$	CH$_3$	H
R'	CH$_3$	CH$_3$	CH$_3$	H	CH$_3$	H
R''	OH	OH	H	OH	H	H
R'''	H	H	H	Cl	OCH$_3$	H
R''''	H	H	OH	H	H	OH

156

Formylation of hepta(N-methylamino)-β-cyclodextrin (**157**) or hepta(N-ethylamino)-β-cyclodextrin (**158**) with FAM (at 0°C for two hours and then at room temperature for a further two hours) afforded the hepta(N-methylformamide) (**159**) and the hepta(N-ethylformamide) (**160**) respectively. The formyl group can be removed adding NaOH (pH = 12): no yields are reported.[26]

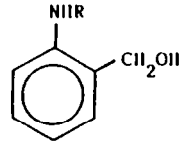


157 R=CH$_3$, R'=H

158 R=C$_2$H$_5$, R'=H

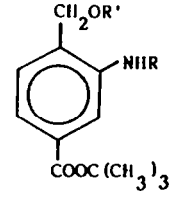
159 R=CH$_3$, R'=CHO

160 R=C$_2$H$_5$, R'=CHO



161 R=H

163 R=CHO

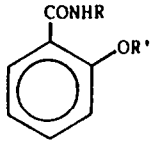


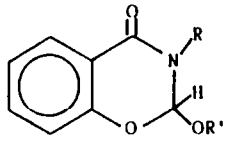
162 R=H, R'=H

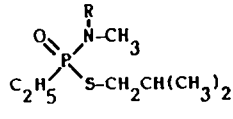
164 R=CHO, R'=H

165 R=CHO, R'=CHO

Different results were obtained in the treatment of the two closely related 2-aminobenzyl alcohols **161**[88] and **162**[74] with AFA. The former, treated with **1** in hexane–ether at 0°C (1.5 h), gave the corresponding formamide (**163**, 90%). The latter was treated with **1** in the presence of pyridine at 0°C (18 h): the reaction mixture contained products of N-formylation (**164**) and N,O-diformylation (**165**). These results are not easily rationalized and an even more confusing pattern arises from experiments with salicylamide (**166**), where the nature of the substrate and the reaction conditions may lead to cyclization and the incorporation of three acyl groups from AFA.[134] The heat sensitive O-formylsalicylamide (**167**) may be obtained by the action of **1**, using pyridine as a catalyst (53% yield). By simply raising the reaction temperature to 20°C (using sodium acetate or very small amounts of pyridine) the product outcome changed to 2-formyloxy-3-formyl-2,3-dihydro-1,3-benzoxazin-4-one (**168**, 41%). In the same conditions, but with larger amounts of pyridine, the 2-acetyloxy derivative (**169**) was isolated (62%). Analogously, the 2-acetyloxy-3-acetyl derivative (**170**, 37%) was obtained starting from N-acetylsalicylamide (**171**): a collateral product formed







166 R=H, R'=H
167 R=H, R'=CHO
171 R=Ac, R'=H
172 R=Ac, R'=Ac
173 R=CHO, R'=H

168 R=CHO, R'=CHO
169 R=CHO, R'=Ac
170 R=Ac, R'=Ac

174 R=H
175 R=CHO

in equal amount was N,O-diacetylsalicylamide (**172**). Compound **167** rearranged quickly to N-formylsalicylamide (**173**), which, in turn, could be transformed to **168** by AFA and pyridine below 5°C (75% yield).[134]

6.2.4. *Sulfonamides.* It was found that AFA in acetic acid and chloroform at room temperature was successful (yields ranging from 71 to 88%) in N-formylating N-phenyl aromatic and aliphatic sulfonamides. However, this reaction surprisingly failed with N-methyl derivatives.[133]

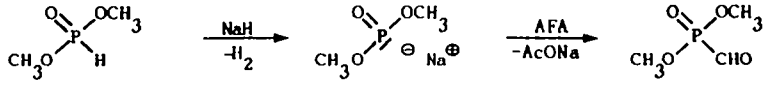
6.2.5. *Phosphonamines.* The secondary amino group of a phosphonamine **174** was formylated at 0°C (95 h) to **175** in the last step of a patented preparation of a pesticide.[42]

6.3. *S-Formylations*

Few results have been reported on the S-formylation of thiols. One is perhaps of lesser applicative interest because formyl fluoride was the formylating agent.[95] S-formylation was observed when thiophenol or methanethiol were treated with excess FAM followed by basic work up and distillation: no yields were reported.[12]

6.4. *P-Formylations*

The sole example of formylation of organophosphorous compounds is reported by Vasella. Dimethylphosphite (**176**) and sodium hydride reacted with AFA in dry ether at −10°C to 20°C for



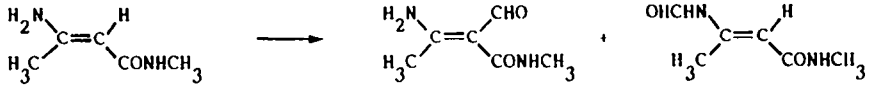
176 178 177

45 min, yielding distilled formylphosphonate dimethyl ester (**177**, 47%). The strong base NaH extracted the hydrogen as a proton from **176** to provide the active nucleophile **178**.[143]

6.5. *C-Formylations*

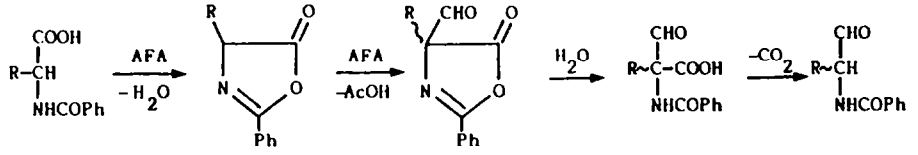
Only a few cases of C-formylations have been reported. Indole derivatives react with AFA and FAM undergoing C-formylation in position-3 as described in Section 6.2.1.[20]

The enamine (**179**) is acylated at C_2 by AFA (**180**, 58%) : another product is the 3-formylamino



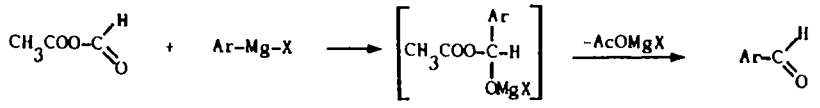
179 180 181

derivative (**181**, 19%).[128] **1** was found[157] to be effective in the C-formylation of α-benzoylamino acids in the presence of TEA and 4-dimethylaminopyridine. The reaction is assumed to follow the mechanism reported below:



R = CH_3, C_2H_5, $(CH_3)_2CHCH_2$

The reaction of AFA and aromatic Grignard reagents[38] (**182**) was of particular interest because it gave only carbonyl products (**183**) without alcohol formation. The aldehyde was one of the two



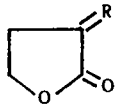
1 182 184 183

possible carbonyl reaction products in every instance. Success in the aldehyde synthesis appeared to depend principally on two factors: (i) preferential addition of the Grignard reagent to the formyl group rather than to the acetyl group and (ii) a good degree of stability of the resulting complex (**184**). The reaction was performed at low temperatures (−70°C). Aldehydes predominated decidedly over ketones when diethyl ether was used as solvent (see Table 14). This predominance may be attributed to the electronic and steric differences between a hydrogen atom and a methyl group which favoured nucleophilic attack by R^- on the formyl carbon. The aldehyde/ketone ratio dropped sharply when tetrahydrofuran replaced diethyl ether, but without significant change in total quantity of carbonyl products. When aliphatic Grignard reagents were used there was substantial alcohol formation.[38]

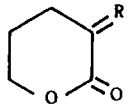
C-Formylations by AFA in THF with N-butyllithium at low temperatures (−10°C then cooled to −78°C) has been reported for a number of cyclic esters. Excellent yields of α-formyl lactones (**185–8a**) were obtained from **185–8b**. For other cases, as for the substrates **189b** and **190b**, lower yields were ascribed to an insolubility of the enolates. This drawback was circumvented in part by

Table 14. Reaction between aromatic Grignard reagents and pure AFA[38]

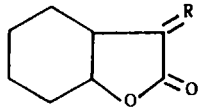
Aryl	Molar ratio AFA : RMgBr	Solvent	Temperature (°C)	Products molar ratios Aldehyde (%)	Ketone (%)
Phenyl	1 : 1	ether	−70	82.9	17.1
2-Methylphenyl	1 : 1	ether	−70	97.1	2.9
3-Methylphenyl	1 : 1	ether	−70	97.1	2.9
4-Methylphenyl	1 : 1	ether	−70	97.7	2.3
3-Chlorophenyl	1 : 1	ether	−70	100.0	0.0
Phenyl	1 : 1	THF	−70	53.5	46.5
Phenyl	2 : 1	ether	−70	85.2	14.8
4-Methylphenyl	2 : 1	ether	−70	97.8	2.2
Phenyl	1 : 1	ether	0	84.0	16.0



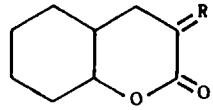
185a,b



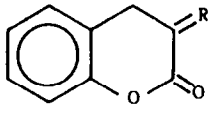
186a,b



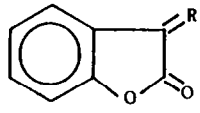
187a,b



188a,b



189a,b

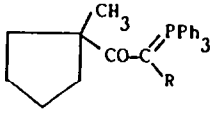


190a,b

a R = CHOH

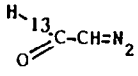
b R = H_2

reacting the lithium enolate of **189b**, but the yield was not satisfactory and **190b** did not react.[63] Formylation of 1-(1-methylcyclopentyl)-2-(triphenylphosphoranyliden)ethanone (**191**) in toluene



191 R=H

192 R=CHO



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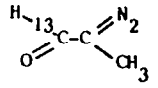
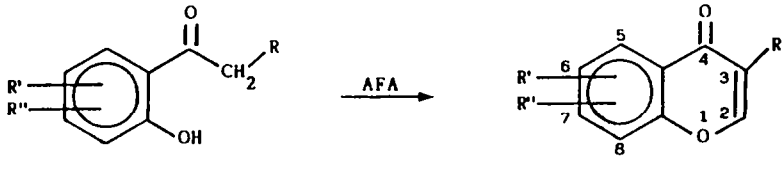


194

by **1** yielded the aldehyde (**192**, 40%).[79] Carbonyl-^{13}C-diazoacetaldehyde (**193**) was obtained from ^{13}C-formyl-AFA and diazomethane in unreported yields.[158] Analogously, 2-diazopropanol (**194**) was obtained in 56% separated yield by reacting diazoethane at −30°C with **1**.[159]

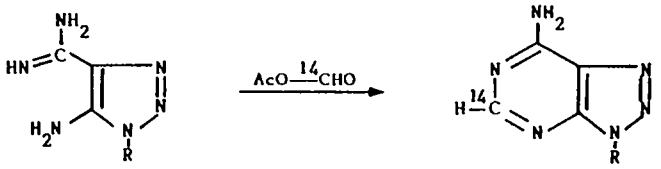
6.6. *Cyclization reactions*

Substituted phenols (**195**, see also Section 6.6.1.) were cyclized at room temperature using AFA to chromones (**196**) according to the general reaction:



195 196

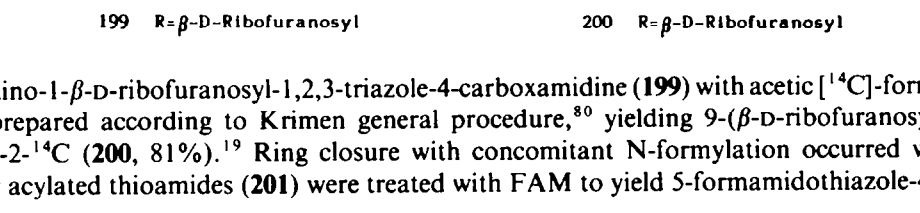
Aroyl chromones,[106] 3-nitrochromones, 3,6-dinitrochromones, 3-acetylchromones, 3-benzoylchromones, 3-methylsulfinylchromones and 3-methylsulfonylchromones were obtained in fairly good yields.[15,16] Quinazolinocarboline alkaloids, such as rutaecarpine, were synthesized by cyclization with **1**, as already discussed in Section 6.2.1.[21] 5-Amino-1,2,3-triazole-4-carboxamidine (**197**) reacted with labeled $^{14}C_{formyl}$-AFA at 70°C giving 8-azaadenine-2-^{14}C (**198**, 77%). The ^{14}C label was incorporated into the 8-azapurine by ring closure of **197**.[89] This ring closure was also performed



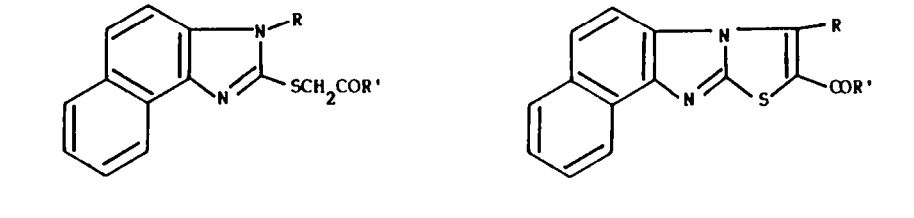
197 R=H 198 R=H

199 R=β-D-Ribofuranosyl 200 R=β-D-Ribofuranosyl

on 5-amino-1-β-D-ribofuranosyl-1,2,3-triazole-4-carboxamidine (**199**) with acetic [^{14}C]-formic anhydride, prepared according to Krimen general procedure,[80] yielding 9-(β-D-ribofuranosyl)-8-azaadenine-2-^{14}C (**200**, 81%).[19] Ring closure with concomitant N-formylation occurred when two suitably acylated thioamides (**201**) were treated with FAM to yield 5-formamidothiazole-4-carboxamides (**202**).[129] The 2-aminothiophenol **203** undergoes cyclization to 6-methoxybenzothiazole (**204**, 49%) by reaction with AFA at 5°C in water.[40] 2-(Acylmethylthio)naphtho[1,2-*d*]imidazoles (**205**) could be N(3)-formylated with FAM in excellent yields to **206**: these products and similar N(3)-



201 R=H, CH_3 202 203 204

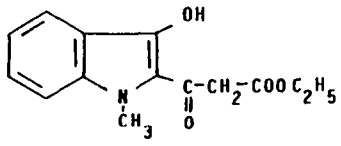


205 R=H

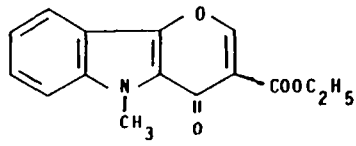
206 R=CHO R'=CH_3, Ph, aryl 208 R=H, CH_3, C_2H_5

207 R=Ac, C_2H_5CO

acyl derivatives (**207**) underwent cyclization when refluxed with sodium acetate and FAM in a 1:2 molar ratio to the corresponding naphtho [1,2′:4,5]imidazo[2,1-*b*]-thiazoles (**208**, 67–97%).[76] AFA and ethyl 3-hydroxy-1-methyl-β-oxo-1H-indole-2-propanoate (**209**) yielded both the cyclization product (**210**, 40%) and **211** (27%).[136] Cyclizations involving salicyclic amide were discussed under Section 5.2.3.[134]



209



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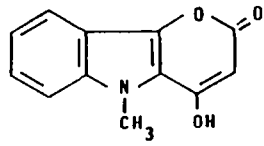

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6.7. *Formylation of metal complexes*

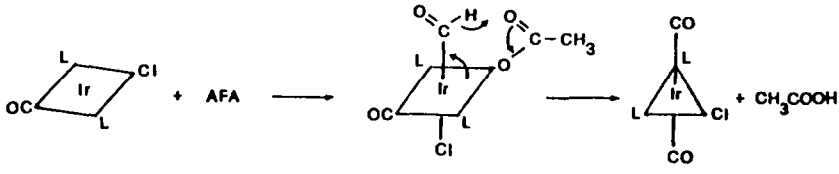
AFA was used as a formylating agent of organometallic complexes of transition metals. Acyl complexes are well known in the synthesis of organotransition metal derivatives whereas the corresponding formyl compounds are rare. The first kinetically stable neutral formyl complex was isolated and characterized by Collman:[30] the formyl tetracarbonylferrate ion (**212**) was formed by the reaction of sodium tetracarbonylferrate (**213**) with **1** in THF at room temperature (25°C) under argon. The reaction of acetic [^{13}C]-formic anhydride with sodium pentacarbonylmanganate (**214**) proceeds rapidly at 0°C to give ^{13}CO-substituted pentacarbonylmanganese hydride (**215**) as the main reaction product and the decacarbonyldimanganese **216** as another product.[45] An unstable formyl complex (**217**) was the intermediate on the way to **215**. By using labeled **1** the authors demonstrated that the reaction pathway involved the effective nucleophilic attack by **214** generating the unstable formyl complex **217**. This, eventually, underwent decarbonylation giving the corresponding pentacarbonyl hydride (**215**) which finally gave the neutral dimer **216**.[45] Quantitative mass spectrometric analysis of the reaction products with $^{13}C_{formyl}$-AFA and the efficiency of ^{13}C-incorporation gave results consistent with this pathway.[113]

$$\underset{213}{(Na^+)[Fe(CO)_4]^{2-}} \xrightarrow[-AcONa]{AFA} \underset{212}{(Na^+)[HOC\text{-}Fe(CO)_4]^-}$$

$$\underset{214}{(Na^+)[Mn(CO)_5]^{2-}} \xrightarrow[-AcONa]{AcO\text{-}{}^*CHO} \underset{217}{[HO^*C\text{-}Mn(CO)_5]} \xrightarrow{-CO} \underset{215}{HO^*C\text{-}Mn(CO)_4} \xrightarrow[-H_2]{+215} \underset{216}{Mn_2(^*CO)_2(CO)_8}$$

Oxidative addition of AFA was examined further in the transition metal series rhodium, ruthenium, iridium, palladium and platinum triphenylphosphine complexes in benzene at room temperature. Although the formyl complexes may be formed as unstable intermediates, no neutral formyl complex could be isolated and metal carbonyl hydrides or their dimers were formed. Platinum and palladium complexes did not undergo oxidative formylation whereas $Rh(PPh_3)_3Cl$, $Ru(NO)(PPh_3)_2Cl$ with an equimolar amount of **1** yielded the monocarbonyl complexes: $Rh(CO)(PPh_3)_2Cl$ and $Ru(CO)(NO)\text{-}(PPh_3)_2Cl$.[33]

Two equivalents of AFA at 25°C added rapidly to the square-planar *trans*-$[IrCl(CO)L_2]$ (**218**, L=PPh_3 or PMe_2Ph) leading to the *cis*-dihydrido-*trans-tertiary*-phosphino complex $IrClH_2(CO)L_2$. The formyl metal product resulting from simple oxidative addition of **1** was not observed. Initial



218 219 220

interaction involved addition of **1** to the *trans*-iridium complex **218** giving a formyl acetato iridium(III) complex (**219**). This species then underwent a rapid internal rearrangement eliminating acetic acid and producing the dicarbonyl species **220**.[139]

6.8. *Miscellaneous reactions*

AFA reacts with anhydrous HF to yield formyl fluoride (68% separated yield) accompanied by variable amounts of acetyl fluoride.[95] Olah and Kuhn found that only acetyl derivatives were the outcome of the reaction between **1** and aromatic substrates in the presence of dialuminium hexachloride: the observation was not accompanied by experimental details. Evolution of carbon monoxide accompanied the reaction. Later, Edwards and Sibille[39] confirmed the absence of aldehydes in Friedel–Craft reactions between **1** and aromatic as well as heteroaromatic substrates. These results may be rationalized in terms of a preliminary complexing of the more electron rich carbonyl oxygen, resulting in the activation of this group in the acyl transfer.

6.9. *Halo- and thio-derivatives*

A survey of the published literature did not reveal any thio- or halo-derivative of AFA. It was found that an equimolecular mixture of anhydrous formic acid and trifluoroacetic anhydride acted both as a N-formylating and trifluoroacetylating agent (Table 15).[52] The results may be interpreted only on the basis of the formation of the mixed anhydride. The electron withdrawing properties of the CF_3 group provide an important influence upon reactivity. This anhydride was found to be thermally labile (loss of CO).

Table 15. Reaction of amines with a trifluoroacetic anhydride–formic acid mixture[a,52]

Amine	Excess reagent[b]	Products (rel %):[c] formamide	trifluoroacetamide
3-Fluorobenzeneamine	acylating mixt.	1	99
Benzeneamine	acylating mixt.	100	0
Benzeneamine	amine	100	0
Benzylamine	acylating mixt.	8	92
Benzylamine	amine	3	97
Cyclohexylamine	acylating mixt.	9	91
Cyclohexylamine	amine	11	89
N-Methylcyclohexylamine	acylating mixt.	100	0
N-Methylcyclohexylamine	amine	100	0
t-Butylamine	amine	100	0

[a] Formic acid (98%) was added dropwise to one equivalent of freshly distilled, acid free, trifluoroacetic anhydride under stirring in inert atmosphere at −20°C. The obtained mixture was used 30 min at −20°C after completion of the mixing of the reagents. It was advisable to dilute the anhydride with an inert dry solvent like chloroform or toluene to moderate the strongly exothermal reaction.

[b] The acylating mixture at −20°C was added very rapidly under stirring to a solution of the amine in chloroform or toluene.

[c] The relative yield is approximately evaluated by first separating the two amides by GC and then evaluating peak area ratios.

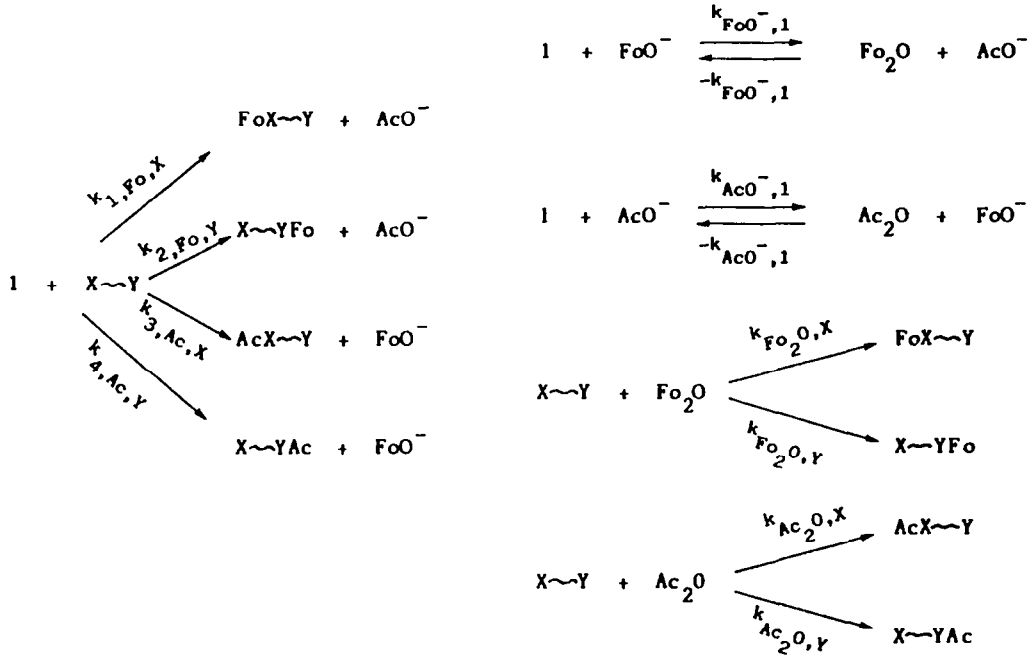
7. DANGEROUS PROPERTIES AND TOXICOLOGY

The adverse effects on human health caused by some kind of contacts with AFA (and any formic mixed anhydride) were not investigated directly, but could be inferred. The compound is more irritating than acetic anhydride and being more volatile the chances of inhalation are stronger. Eye and skin protection are therefore mandatory. Decomposition to a gaseous poisonous product, carbon monoxide, is to be foreseen; therefore, tightly stoppered containers should be avoided.

8. MISCELLANEOUS REMARKS

The knowledge of this simple compound seems to be rather scant. The pure compound is stable thermally both in the condensed and the gas phase.[43,46,111] Even traces of acids and bases can start irreversible changes. One has not to forget that glass itself is not inert[111] and distillation apparatus of another nature may be more suitable.

The reactivity pattern has not been adequately studied. The few studies available were not always carried out with the now contemporary and accurate analytical techniques and, more importantly, with AFA of precisely defined purity. Apart from our data (see Section 4), not a single batch of **1** has ever been analyzed by GC. Acetylation vs formylation and acylation regioselectivity, when observed with close to stoichiometric ratios of **1** vs substrate and after long times, do not cast light on the intrinsic reactivity pattern of **1**, if one keeps the reactions of Scheme 1 in consideration. It is likely that as the concentrations of AcO^- or FoO^- will increase, some Ac_2O or Fo_2O might be formed, which will interfere with the observation, which, therefore, must be performed either at very short times or with a very large excess of pure **1**. If 'catalysts' are used, the study must foresee the observation of the nature and stability of the adduct AFA-catalyst.



Scheme 1. Ac- vs Fo-ation and X vs Y regioselectivity.

Among the aprotic syntheses, the use of substrates with newly designed leaving groups may be attractive: one of these, applied to the synthesis of a number of mixed formic anhydrides, employed as a reactant the O-acyl derivatives of polymeric pyridine oxide.[46]

Among few other formic mixed anhydrides, mention could be made of benzoic formic anhydride,[77] which is thermally stable as to be distilled at 69.0°C (80 Pa). Its reactivity was tested against aniline which gave formanilide in unreported yield.[43] The synthesis of this anhydride may be improved and adapted to some derivative yielding a solid mixed formic anhydride.

In 1973 a polymeric material[116] was introduced (pop corn polystyrene) with carboxylic functions which can be converted to COCl by the action of oxalyl dichloride; subsequent reaction with benzoic

acid produced the mixed anhydride. Perhaps such a procedure could be applied to formic acid (or some of its metallic salts) to produce a formylating agent of good stability and highly selective reactivity especially when a too reactive nucleophile might be (in part) unable to discriminate between the two carbonyls of **1**.[148]

None of the reactions involving AFA reported to date were either shown or believed to involve radical mechanisms, except, perhaps, for one case.[57]

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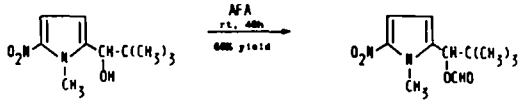
NOTE ADDED IN PROOF

The following experiments with AFA appeared after the completion of the manuscript (Refs through Chemical Abstracts July–December 1988).



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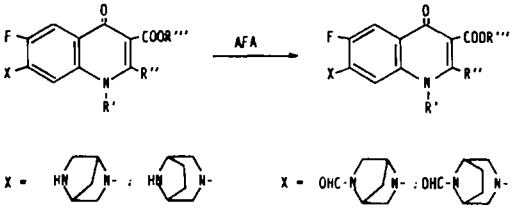

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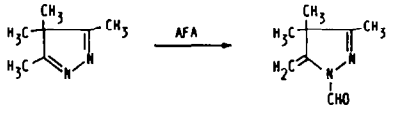

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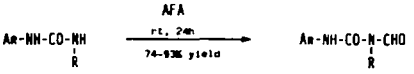

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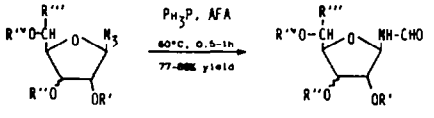

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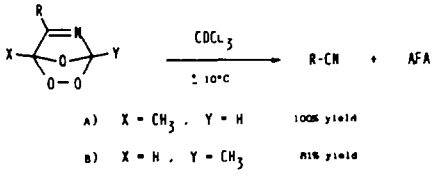

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