New Methods for the Preparation of Aromatic Aldehydes

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This review aims to provide an overview of the use of oligoformylamine derivatives and related compounds as formylating reagents for aromatic compounds. The synthesis of aromatic aldehydes by means of Fries rearrangement of aryl formates is also reported on.

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1. Introduction

From the beginning of organic chemistry until the present day, aromatic aldehydes have played important roles for the development of theoretical ideas in this field. As one example, the radical hypothesis was confirmed with studies on aromatic aldehydes.

However, it is not only from the historical point of view that aromatic aldehydes are of great interest. The development of new preparation procedures for these compounds by C−C bond-forming processes, from the early beginnings of organic chemistry until now, has been and still is a challenge for organic chemists. In contrast to the acylation of

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MICROREVIEWS: This feature introduces the readers to the author's research through a concise overview of the selected topic. Reference to important work from others in the field is included.

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aromatic compounds, which can be readily achieved with the aid of acyl chlorides and Lewis acids by use of Friedel−Crafts techniques, no similar procedures could be used for the formylation of aromatic compounds, since formyl halides were unknown. In earlier times, chemists tried to circumvent this problem by the two following strategies.

On the one hand, C−C bond-forming reactions giving hydroxymethyl- or halomethyl-substituted aromatic compounds were developed, and these were then oxidized further to yield the aromatic aldehydes. Syntheses of aromatic aldehydes by the Duff[1] and Casiraghi[2] approaches are reactions of this type. On the other hand, chemists also tried to find direct formylation reagents as substitutes for the unstable formyl chloride, which should allow direct introduction of the formyl group into the aromatic nucleus. So, in the method of Gattermann and Koch, CO/HCl in the presence of $AlCl_3$ and Cu^ICl is used as formylating reagent system.[3] Since the scope of this procedure was rather small, Gattermann introduced a formylation system of wide scope, consisting of HCN/HCl and $AlCl_3$ or $ZnCl_2$.[4] The adducts formed from formimidoyl chloride (a hetero analogue of formyl chloride) and $AlCl_3$ or $ZnCl_2$, respectively, were thought to be the formylating reagents. Later on the procedure was simplified by Adams, who replaced HCN and $ZnCl_2$ by $Zn(CN)_2$. Some 50 years later, Kreutzberger presented another variation, using *s*-triazine/$AlCl_3$ as the formylating reagent. This formylation procedure seemed to be the method of choice for industrial applications. However, industrial use has been restricted due to the fact that 1,3,5-triazine was available only in small amounts and at fairly high prices, since only a few laboratory methods for its preparation were known. Recently a new technical process giving access to technical quantities of *s*-triazine for industrial purposes was developed. Unfortunately, it turned out that the compound is strongly toxic on inhalation and possibly acts as a teratogen.[5]

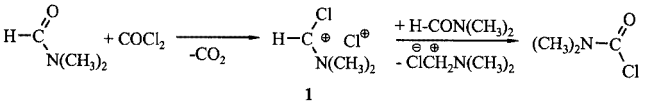
According to Reimer and Tiemann, hydroxyarenes can be formylated by use of chloroform and sodium hydroxide.[6] By addition of long-chain primary or secondary amines to the reaction mixture, the yields can be markedly improved.

Vilsmeier and Haack demonstrated that the adduct of *N*-methylformanilide and phosphoryl chloride can act as a formylating reagent for activated aromatic compounds.[7] This formylating reagent has been varied by replacement of *N*-methylformanilide by *N*,*N*-dimethylformamide and of phosphoryl chloride by phosgene, oxalyl chloride, thionyl chloride, phosphorus pentachloride, sulfonyl halides etc. Recently, the adduct of DMF and dichlorophosphorus anhydride was shown to have an enhanced reactivity.[8]

Olah described a simple procedure for the preparation of formyl fluoride, and showed that this compound, in the presence of boron trihalides such as BF_3, BCl_3, or BBr_3, can act as a strong formylating reagent even for simple aromatic compounds such as benzene. The Olah reaction is the only formylation procedure that proceeds analogously to the classical Friedel−Crafts acylation of aromatic compounds.

A formylation method of very broad scope for aromatic and heteroaromatic compounds was introduced by Groß and Rieche. In this process, dichloromethyl methyl ether, activated by aluminium chloride or $SnCl_4$, acts as formylating reagent.[9] All of the classical, direct formylating procedures suffer to greater or lesser degrees from serious drawbacks. In some processes, strongly toxic or etching compounds (carbon monoxide, hydrocyanic acid, phosgene, *s*-triazine, formyl fluoride, hydrogen chloride, phosphoryl chloride etc.) are used. Additionally, some of these compounds are gaseous, while some (e.g., formyl fluoride) are not stable on storage and therefore are not easy to handle and to dose. In all of the aldehyde syntheses mentioned above the last step is a hydrolysis reaction, which can give rise to problems with waste water. This question is of special importance if Vilsmeier−Haack reactions are performed with DMF/$POCl_3$: hydrolysis of the reaction mixtures affords phosphorous acid, which is an environmental problem. Similar problems sometimes arise in the Groß−Rieche reaction, because some formylations need excessive activators (up to 4 mol $SnCl_4$ per mol dichloromethyl methyl ether).

If the Vilsmeier−Haack reaction is performed on industrial scales with DMF/phosgene, one needs special safety procedures and apparatus, because the *N*,*N*-dimethyl(chloromethylen)iminium chloride (**1**), formed from DMF and phosgene, is known to react with *N*,*N*-dimethylformamide to give the strongly carcinogenic *N*,*N*-dimethylcarbamoyl chloride.



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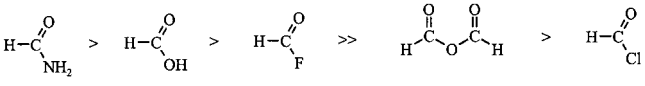
To the best of our knowledge the Groß−Rieche formylation has found no industrial application. Industrial chemists used to suspect that the dichloromethyl methyl ether was always contaminated with chloromethyl methyl ether − an extremely strong carcinogen.

Against this background it seemed desirable to develop new formylation procedures for aromatic compounds. The reagents used should fulfil the conditions of being: (i) easy to prepare from simple, inexpensive chemicals, (ii) stable on storage, (iii) easy to handle and to dose, (iv) low in volatility, and (v) non-toxic or of low toxicity.

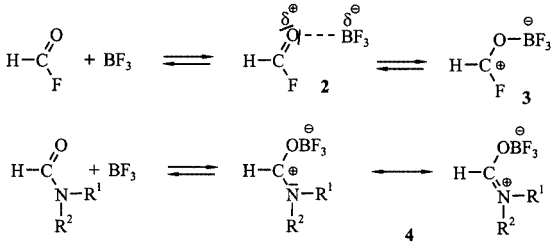
2. Synthesis of New Formylating Reagents for Aromatic Compounds

The stabilities of formic acid derivatives decrease in the following order:



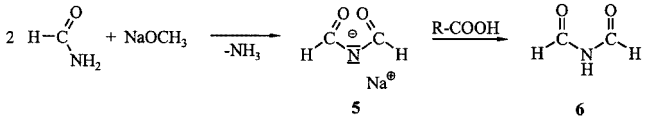
Obviously, the stabilities of the compounds seem to depend on the nucleophilicities of the substituents attached to the formyl group.

The fairly stable formyl fluoride shows high reactivity in the Friedel−Crafts-analogous Olah formylation,[3f,10] since the formyl carbon atom in its adducts with boron trifluoride (**2** and **3**) is highly electropositive as a consequence of the strong −*I*-effect of fluorine. Similar adducts **4** of formamides are only of low electrophilicity, because the positive charge on the carbon atom is reduced by the +*M*-effect of the amino group.



The reactivities of formamide−Lewis acid adducts should increase if the hydrogen atoms at the amide nitrogen atom are replaced by strongly electron-attracting acyl groups. In order to avoid the undesired by-products often observed if mixed substituted compounds (e.g., acetic formic anhydride) are involved in reactions, only diformylamine (diformamide, **6**) and triformylamine (triformamide, **8**) merited consideration.

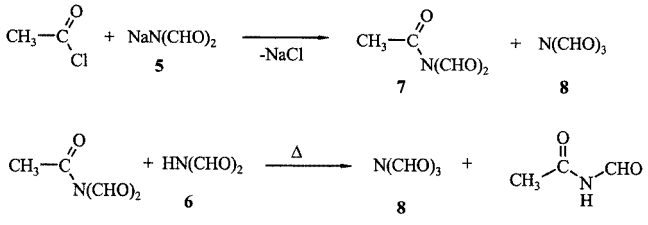
The sodium salt of diformamide **5** was first described in 1913,[11] and its preparation has been greatly simplified in recent decades.[12−14] Diformamide can be obtained from sodium diformamide on acidification with acetic acid.[12]



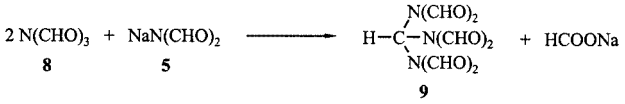
Sodium diformamide (**5**), prepared on larger scales from formamide and sodium methoxide by literature procedures, is usually contaminated with formamide or sodium methoxide. The content of the latter species reduces the yields of subsequently prepared compounds, such as triformamide.

In our experience, pure **5** and pure **6** can be obtained if sodium methoxide is replaced by sodium ethoxide and acetic acid by formic acid in the acidification step. It is also advantageous to take up the diformamide from the reaction mixture in THF rather than diethyl ether.

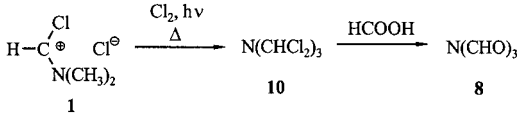
Sodium diformamide reacts with acetyl chloride to give *N*,*N*-diformylacetamide (**7**); a by-product (up to 10% yield) is triformamide (**8**). Heating of *N*,*N*-diformylacetamide with **6** affords triformamide (**8**) in good yields.[15]



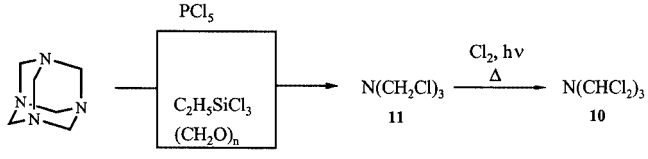
Tris(diformylamino)methane (formyl-aalen) (**9**) can be prepared from triformamide **8** and sodium diformamide (**5**).[16] Formyl-aalen is a remarkable compound, since its entire set of carbon atoms solely possess the oxidation state of formic acid.



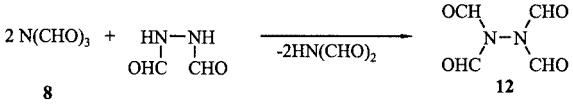
Triformamide (**8**) can also be prepared from tris(dichloromethyl)amine (**10**) by formolysis.[17] Tris(dichloromethyl)-amine (**10**) is accessible by photochlorination of the iminium salt **1** (obtained from DMF and phosgene).[17]



We have developed another way to prepare **10**, starting from tris(chloromethyl)amine (**11**). The tris(chloromethyl)-amine (**11**) required is formed in the reaction between hexamethylenetetramine and phosphorus pentachloride.[18−20] The same compound can also be obtained by treatment of hexamethylenetetramine with trichloro(ethyl)silane and paraformaldehyde in the presence of catalytic amounts of trifluoromethanesulfonic acid. Photochlorination of tris(chloromethyl)amine (**11**) affords **10** in good yields.



Tetraformylhydrazine (**12**) is readily prepared by heating triformamide (**8**) with *N*,*N*′-diformylhydrazine,[21] the compound having been characterised by X-ray crystal structure analysis.[22]

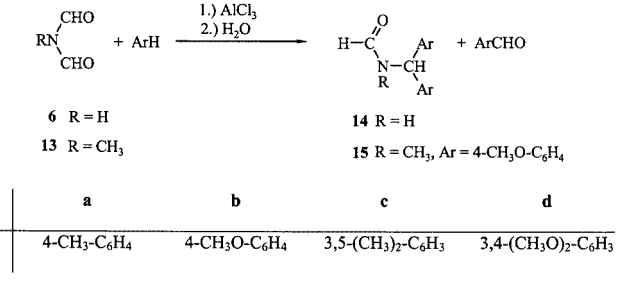


3. Formylation Reactions With Adducts of Diformamide and Lewis Acids

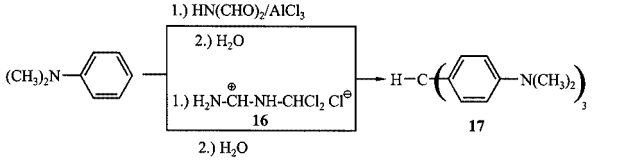
As mentioned above, in the well-known Vilsmeier−Haack chemistry, reactive adducts of *N*,*N*-disubstituted formamides and acylation reagents [$POCl_3$, RCOCl, $COCl_2$, $(COCl)_2$, RSO_2Cl, PCl_3, PCl_5, $SOCl_2$ etc.] are used for formylation reactions. In contrast, the reactivity of adducts formed from acid amides and Lewis acids is poorly documented, and there are only a few reports confirming that these adducts are also able to formylate aromatic compounds. The formylation of a 3-hydroxybenzo[*b*]thiophene derivative by formamide/$AlCl_3$ is described in a patent.[23] In a study concerned with the reactivity of adducts of *N*,*N*-dimethylformamide and acylation reagents, or protonic

acids or Lewis acids it is stated that the formylation activity of the *N*,*N*-dimethylformamide−boron trifluoride adduct is rather low.[24] The reactivities of adducts of *N*,*N*-disubstituted formamides and $POCl_3$ depend strongly on the N-substituents, as revealed by comparative reactivity studies. Thus, the *N*-methyl-*N*-phenyl(chloromethylen)iminium ion is more than five times as reactive as the analogous *N*,*N*-dimethyl(chloromethylen)iminium compound.[25]

Against this background, adducts of Lewis acids and diformamide (**6**) should possess enhanced reactivities towards aromatic compounds. In the presence of aluminium chloride, diformamide (**6**) reacts at 60−70 °C with aromatic compounds such as toluene, anisole, *m*-xylene, and veratrole to give *N*-(diarylmethyl)formamides **14** in good yields. Unfortunately, aromatic aldehydes are formed only as by-products, and in low yields (up to 4%).[26]



14	a	b	c	d
Ar	4-CH_3-C_6H_4	4-CH_3O-C_6H_4	3,5-$(CH_3)_2$-C_6H_3	3,4-$(CH_3O)_2$-C_6H_3



The best yields are obtained if $AlCl_3$ and diformamide are used in a molar ratio of 2:1 and the aromatic compound is used in excess (either 5 mol-equiv. based on diformamide or as the solvent). Chlorobenzene or carbon disulfide can also serve as solvents. Attempts to improve the yields of the aldehydes by changing the molar ratio of the reacting compounds or by using other Lewis acids [$Yb(CF_3SO_3)_3$, $FeCl_3$, BF_3, $TiCl_4$, $ZnCl_2$, $SiCl_4$, $SnCl_4$, $POCl_3$] or other solvents such as nitromethane, dichloromethane, diethyl ether, and cyclohexane were unsuccessful.[26]

Tris(4-dimethylaminophenyl)methane (**17**) is obtained from *N*,*N*-dimethylaniline and diformamide/$AlCl_3$ after hydrolysis.[26] Interestingly this compound was also the product, when the "sesquichloride of hydrocyanic acid" **16** was allowed to react with *N*,*N*-dimethylaniline by Gattermann and Schnitzspahn.[27]

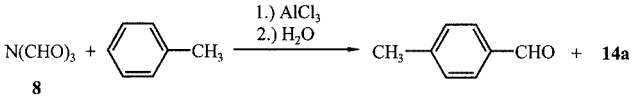
N-Methyldiformamide (**13**) behaves in principle as diformamide, since *N*-[bis(4-methoxyphenyl)methyl]-*N*-methylformamide (**15**) was obtained from anisole and *N*-methyldiformamide/$AlCl_3$.[26]

Obviously, the structurally unknown intermediates formed from the diformamide/$AlCl_3$ adduct and the aromatic compound is more reactive than the diformamide/$AlCl_3$ adduct itself. This should not be the case with triformamide as the formylating reagent.

4. Formylation of Aromatic Compounds with Triformamide (8)[26]

Treatment of triformamide (**8**) with toluene in the presence of aluminium chloride (molar ratio 0.5:5:1.5) at 9 °C revealed that one formyl group of triformamide is of extremely high reactivity.

When the triformamide/$AlCl_3$ adduct has reacted with toluene to give tolualdehyde, it splits off diformamide, which reacts with toluene to give the *N*-[bis(*p*-tolyl)methyl]-formamide **14a** as described above. The reaction afforded (*o*,*p*)-tolualdehydes in 79% yield; additionally *N*-[bis(*p*-tolyl)-methyl]formamide (**14a**) was obtained in 93% yield (calculated in relation to the diformamide formed during the formylation process).



If the same reaction is performed in the molar ratio triformamide/toluene/$AlCl_3$ (1:1:1), the only isolated reaction products are (*o*,*p*)-tolualdehyde (yield 55%). Similar results were obtained in the formylation of anisole.

The aldehydes listed in Table 1 could be prepared by this procedure.

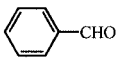
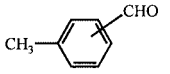
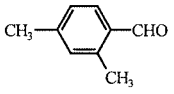
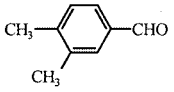
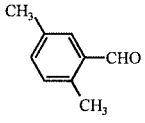
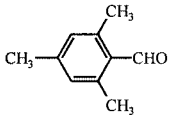
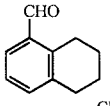
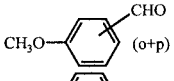
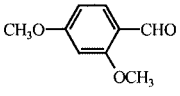
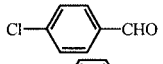
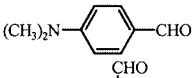
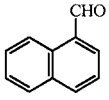
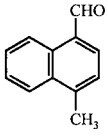
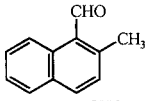
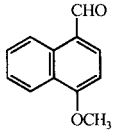
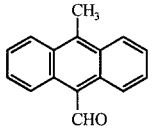
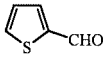
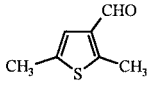
The yields reported in Table 1 were usually obtained in the first run. Hydroxyarenes such as phenol, and acid-sensitive heterocycles such as furan or pyrrole could not be formylated by triformamide/$AlCl_3$. In the case of the latter two compounds the reaction mixtures form resinous products. Electron-deficient heterocycles such as quinoline or 1,3-benzothiazole are not attacked by the triformamide/$AlCl_3$ system, whereas phenothiazine is formylated at the nitrogen atom, as is also the case with the Vilsmeier−Haack reagent.[28]

From the formylation reactions of anisole, toluene, *o*-xylene, *m*-xylene, mesitylene, and *N*,*N*-dimethylaniline, which were performed under various conditions and with use of different Lewis acids, the following conclusions can be deduced:

(i) Nonpolar solvents such as carbon disulfide, as well as strongly polar solvents such as nitromethane, nitrobenzene, and chloroform, seem to slow down or suppress the formylation reaction, whereas weakly polar solvents such as chlorobenzene or 1,2-dichloroethane and even 1,1,2,2-tetrachloroethane are suited for the formylation process.

(ii) As is to be expected, the nature of the Lewis acid strongly influences the course of the reaction, since the strength of the Lewis acid is important for the electrophilicity of the adduct formed from it and triformamide. On the other hand, the acidity of the Lewis acid also seems to determine the amount of the by-products formed.

Table 1. Aromatic aldehydes by formylation of aromatic compounds with triformamide/$AlCl_3$ (molar ratio 1:1:1)

Aromatic compound	Reaction conditions temp. [°C]/time [h]	Aromatic aldehyde	Yield (%)
benzene	5–10/15		34
toluene	0/2 → 20/48		55 ($o/p \approx 1:9$)
m-xylene	20/3 −15 → 20/15		16 resp. 43[a]
o-xylene	−15 → −6/14		29[a]
p-xylene	−15 → −10/14		19[a]
mesitylene	−15/24		34 resp. 52[b]
1,2,3,4-tetrahydro-naphthalene	3/0.5 20/4		16[c]
anisole	2-5/4 or 0/2 → 20/48		56 65
1,3-dimethoxy-benzene	3/0.5 and 20/4		50
chlorobenzene	30/1 and 50/13		1[d]
N,*N*-dimethyl-aniline	5/1 and 20/3		19[e]
naphthalene	10/5 20/17		18
1-methyl-naphthalene	3/1[a] 20/6		30
2-methyl-naphthane	3/3 20/17		25[f]
1-methoxy-naphthalene	3/0.5 20/17		42
9-methyl-anthracene	3/1 20/15		62[g]
thiophene	40/0.1[h]		18[i]
2,5-dimethyl-thiophene	3/0.5 20/1		30

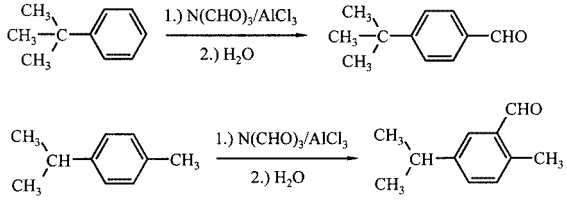
[a] Molar ratio aromatic compound/triformamide/$AlCl_3$ (1:1:2). [b] The higher yield is obtained when the molar ratio is changed to aromatic compound/triformamide/$AlCl_3$ (1:2:2). [c] Small amounts of transalkylation occur. [d] Yield determined from ^1H NMR spectrum. [e] Small amounts of tris(4-dimethylaminophenyl)methane are a by-product. [f] The product is contaminated by two other isomers. [g] Molar ratio aromatic compound/triformamide/$AlCl_3$ (1:2:2). [h] The reacting compounds are mixed at −20 °C. [i] Resinous material is obtained as by-product.

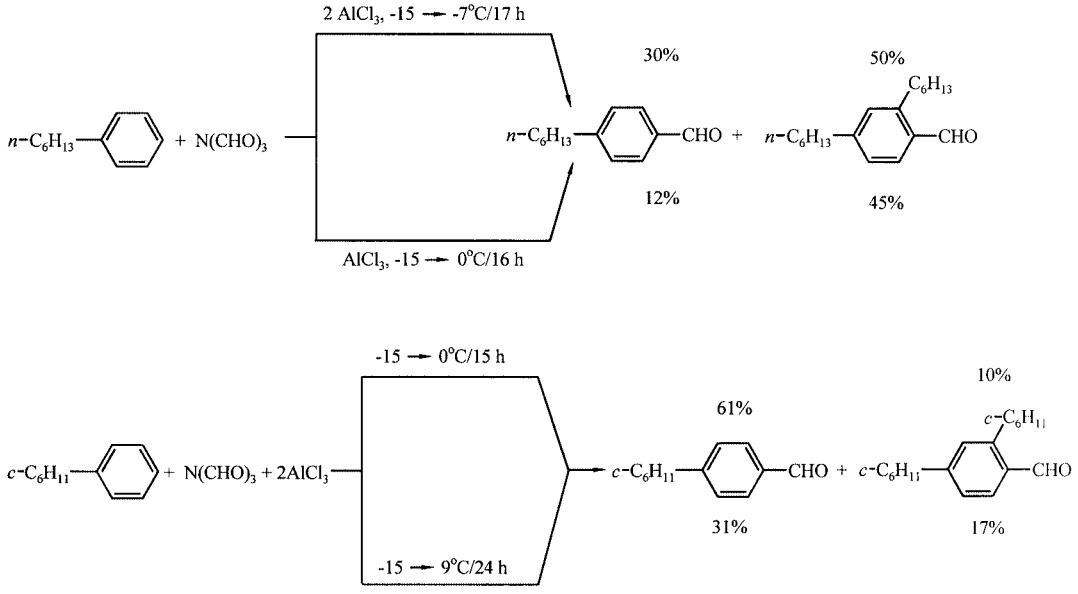
In general, $AlCl_3$, $AlBr_3$, BCl_3, and BBr_3 are well suited for the activation of triformamide, the bromo compounds appearing to be more effective than the corresponding chloro compounds. At least in the formylation of alkoxyarenes (e.g. anisole), and with the exception of $AlCl_3$, strong Lewis acids which are aldehyde-selective in Kobayashi's terms,[29] such as $FeCl_3$, $TiCl_4$, or $SnCl_4$, are not well suited as activators for triformamide. For the formylation of strongly activated aromatic compounds such as *N*,*N*-dimethylaniline, the boron trifluoride−diethyl ether adduct can be used to activate the triformamide.

(iii) To obtain good yields of aldehydes, the molar ratio of triformamide/$AlCl_3$ or triformamide/BCl_3 should be ca. 1:2 and the formylation process should be started at temperatures between −40 to −15 °C, depending on the individual case. If the compound to be formylated is not expensive, it should be used in excess or as solvent.

The rules given above should be seen only as approximate guidelines. In our experience, a few experiments are usually necessary in order to obtain the "optimal" yields for the desired aldehyde in a particular formylation problem, in which special emphasis should be concentrated on the solvents and on the applied reaction temperatures.

The formylation of aromatic alkane compounds by the Gattermann−Koch approach is applied on industrial scales. In the laboratory, however, this procedure is hard to use, since pressures of 100 bar are necessary to obtain good yields of aldehydes. With the aid of triformamide/$AlCl_3$ this problem can be obviated, so *tert*-butylbenzene can be formylated to give 4-*tert*-butylbenzaldehyde, and 5-isopropyl-2-methylbenzaldehyde can be obtained analogously from *p*-cymene.



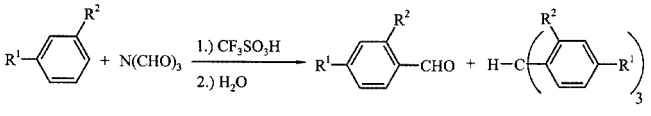


The formylation of longer chain alkyl- or cycloalkyl-substituted benzenes with triformamide/$AlCl_3$ is accompanied by transalkylations. From hexylbenzene and cyclohexylbenzene, distillation-separable mixtures of 4-hexylbenzaldehyde and 2,4-dihexylbenzaldehyde or 4-cyclohexylbenzaldehyde and 2,4-dicyclohexylbenzaldehyde, respectively, were obtained on treatment with triformamide/$AlCl_3$. The ratio in which monoalkylbenzaldehydes and 2,4-dialkylbenzaldehydes are formed depends on the stoichiometric amount of aluminium chloride and the applied reaction conditions. Increasing amounts of aluminium chloride and prolonged reaction times at higher reaction temperatures seem to favour the formation of the 2,4-disubstituted aldehyde.

These results can be viewed as analogous to the well-known fact that alkyl groups can migrate in the course of acylations of monoalkylbenzenes by Friedel−Crafts techniques.[30,31] Even in the Gattermann−Koch formylation of diisopropylbenzene, the formation of a mixture of 4-isopropylbenzaldehyde, 2,4-diisopropylbenzaldehyde, benzaldehyde, and diisopropylbenzenes was observed.[32]

Triformamide can also serve as a formylating reagent in the presence of trifluoromethanesulfonic acid. On addition of trifluoromethanesulfonic acid to a mixture of toluene, triformamide, and chlorobenzene (solvent) at −15 °C, aldehyde yields of 17% and 50% were obtained after 20 h reaction time (at −15 to 20 °C), when the reacting compounds were used in molar ratios of toluene/triformamide/trifluoromethanesulfonic acid of 1:1:1.5 and 2.3:1:12.9, respectively. The amount of trifluoromethanesulfonic acid can be reduced to nearly a third of the value given above (molar amount 2.3:1:4.6) without significant decrease in the aldehyde yield (46%). Trifluoromethanesulfonic acid can be replaced in the formylation reaction by perfluorobutanesulfonic acid.

The formylation of 1,3-dimethoxybenzene with triformamide/trifluoromethanesulfonic acid was performed at −10 °C in chlorobenzene, acetonitrile, and nitromethane as solvent. The best result (about 50%) was obtained in nitromethane, when a molar ratio of triformamide/trifluoromethanesulfonic acid from 1:3 to 1:3.5 was chosen. Under similar conditions, anisaldehyde can be obtained from anisole in a yield of 17%. Tris(4-methoxyphenyl)methane was obtained as a side product, together with higher, unidentified condensation products in yields of about 73%.



$R^1 = CH_3$, $R^2 = H$ (yields 17-50%)

$R^1 = OCH_3$, $R^2 = H$ (yields 17%)

$R^1 = R^2 = OCH_3$ (yields 50%)

5. Formylation Reactions with Tris(diformylamino)methane ("Formyl-aalen") (9)[16,33]

Formyl-aalen (**9**) contains six formyl groups. Three of them can be used for the formylation of aromatic compounds after activation with strong Lewis acids such as aluminium chloride.

The formylation of *o*-xylene in 1,2-dichloroethane in the presence of increasing amounts of aluminium chloride (range: 4−12 mol per mol formyl-aalen) was studied, to find out the molar quantities of the Lewis acids (relative to formyl-aalen) needed to obtain good yields of aromatic aldehydes. The results are given in Table 2.

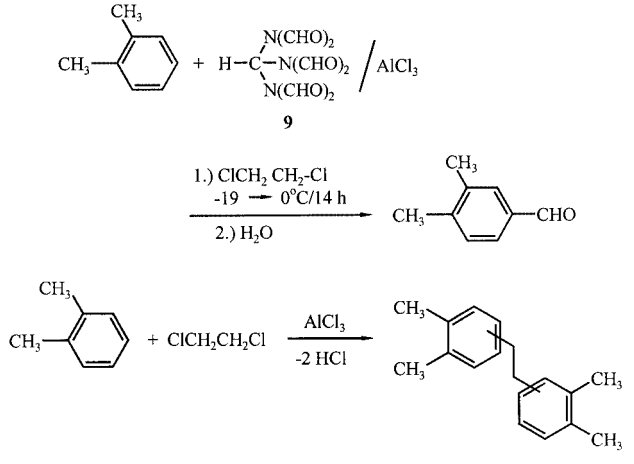
The yields of aldehyde increase if the **9**/$AlCl_3$ ratio decreases. To obtain good yields the ratio of **9**/$AlCl_3$ should be chosen to be between 1:6 and 1:10. In such experiments

Table 2. 3,4-Dimethylbenzaldehyde from tris(diformylamino)methane (**9**) and aluminium chloride in 1,2-dichloroethane (reaction conditions: −19 °C → 0 °C/14 h)

Entry	Molar ratio of the reacting compounds *o*-Xylene	Tris(diformylamino)methane	$AlCl_3$	Yield (%)[a]
1	3	1	4[b]	42
2	3	1	5	46
3	3	1	6[b]	42
4	4	1	5[b]	47
5	4	1	6	59
6	4	1	8	65
7	6	1	6[b]	44
8	6	1	6	63
9	6	1	8	72
10	6	1	10	75
11	6	1	12	64[c]
12	14[d]	1	12	65
13	15.3[d]	1	4	45

[a] The yield was calculated by assuming that **9** delivers three formyl groups. [b] Aged, deactivated aluminium chloride (partially hydrolysed by opening of the stock bottle several times when the compound is removed). [c] By-product is 7% 1,2-bis(dimethylphenyl)-ethane. [d] Without 1,2-dichloroethane; *o*-xylene served as the solvent.

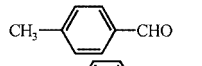
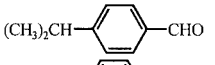
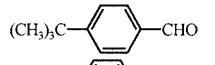
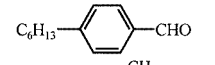
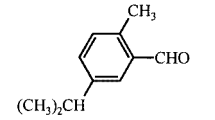
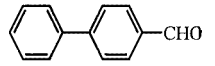
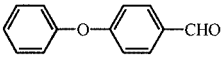
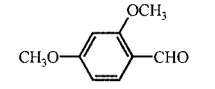
the molar ratio of xylene/**9** should be in the 4:1 to 6:1 range. When, as in the present case, 1,2-dichlorethane was used as solvent, the applied reagent system, consisting of **9**/$AlCl_3$ (1:12), gave rise to the formation of 7% 1,2-bis(3,4-dimethylphenyl)ethanes. Obviously, the excessive amount of $AlCl_3$ induces Friedel−Crafts alkylation of *o*-xylene by 1,2-dichloroethane.



In addition, the yields of the aldehyde decrease although excess *o*-xylene is present. Possibly the hydrogen chloride formed in the Friedel−Crafts alkylation process decomposes the tris(diformylamino)methane. This would explain why the quality of the aluminium chloride strongly influences the result of the formylation reactions. Significantly better yields of aldehydes are obtained with freshly purchased material (compare Entries 7 and 8).

In order to provide an impression of the scope of the new formylation procedure, some aromatic alkane compounds

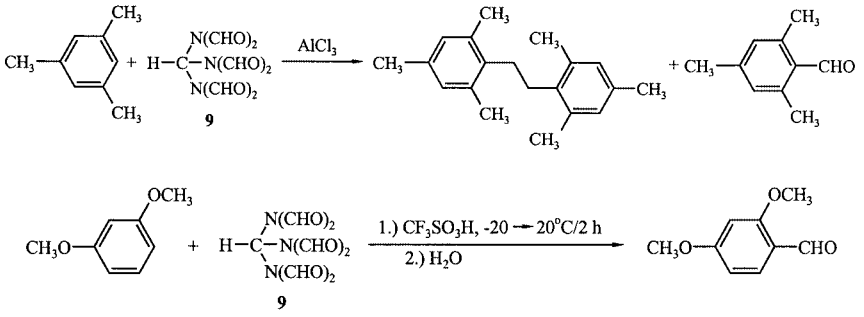
Table 3. Aromatic aldehydes from activated aromatic compounds/tris(diformylamino)methane (**9**)/aluminium chloride (molar ratio 3:1:6) in 1,2-dichloroethane

Aromatic compound	Reaction conditions temp. [°C]/time [h]	Aromatic aldehyde	Yield (%)[a]
toluene	−15 → 0/20		55[b]
cumene	−13 → −1/14		38[c]
tert-butylbenzene	−13 → −1/16		33[d]
hexylbenzene	−15 → −1/15		55[e]
p-cymene	−15 → −3/15		45[f]
diphenyl	−13 → −1/16		54[g]
diphenylether	−13 → +1/16		20[h]
1,3-dimethoxy-benzene	−13 → +2/15 −12 → 0/15		45[i] 67[j]

[a] Yields are calculated by assuming that 1 mol of tris(diformylamino)methane provides three formyl groups. [b] The product contains about 3% *o*-tolualdehyde. [c] The product was purified through the bisulfite adduct. [d] By-product was 1,4-di-*tert*-butylbenzene (9%). [e] The product was contaminated by 5% hexylbenzene. [f] By-products are 2-isopropyl-5-methylbenzaldehyde (7%) and 1,3-diisopropylbenzene (11%). [g] Product contained 6% biphenyl. [h] Product contained 7% diphenyl ether. [i] Product contained 7% 1,3-dimethoxybenzene. [j] Molar ratio dimethoxybenzene/tris(diformylamino)-methane/$AlCl_3$ (6:1:10).

such as toluene, cumene, *tert*-butylbenzene, hexylbenzene, *p*-cymene, and aromatic ethers were treated with formylaalen/aluminium chloride (1:6) under standardized − not optimized − conditions in 1,2-dichloroethane. The results are given in Table 3. The yields of the aldehydes could very probably be significantly improved by raising the amount of aluminium chloride, this assumption having been verified in the case of 2,4-dimethoxybenzaldehyde. The compound was obtained in 67% yield when the molar ratio of the reacting compounds was 6:1:10, compared with a yield of 45% when a molar ratio of 3:1:6 was used. The results show that, in general, tris(diformylamino)methane in combination with aluminium chloride is well suited for the formylation of aromatic alkane compounds and aromatic ethers.

In a further series of experiments we tried to find out which other solvents might be suited for the formylation process with the tris(diformylamino)methane (**9**)/$AlCl_3$ system. *o*-Xylene was thus treated with tris(diformylamino)methane (**9**)/$AlCl_3$ (molar ratio 4:1:8) in the corresponding solvent. Usually the orthoamide was added to the reaction mixture at about −10 °C. The mixtures were stirred at temperatures between −1 and +2 °C for 14−17 h, and then hydrolysed and worked up.



At low temperatures, solvents containing nitro groups seem to suppress the formylation reaction. The aluminium chloride may form a complex with the nitro groups and thus become deactivated. In principle, 1,1,2-trichlorotrifluoroethane and chlorobenzene can also serve as solvents. Carbon disulfide seems to be even better suited, since in the first experiment the aldehyde was obtained with a yield of 40%. The use of CS_2 might be important and advantageous in cases in which halogenated solvents such as 1,2-dichloroethane in combination with Lewis acids interfere in the reaction, giving rise to competition between the Friedel–Crafts alkylation and the formylation reaction. The steric demand of the reactive complex of 1,2-dichloroethane and aluminium chloride is surely less than that of the complex formed from tris(diformylamino)methane and aluminium chloride. In cases in which sterically shielded positions in the aromatic compound are to be formylated, competition from Friedel–Crafts alkylation can become very effective and exceed the formylation reaction even if not much excessive Lewis acid is present. In the formylation of mesitylene with tris(diformylamino)methane/$AlCl_3$ (molar ratio 6:1:8) in 1,2-dichloroethane, therefore, the 2,4,6-trimethylbenzaldehyde is isolated in 18% yield together with 25% of 1,2-bis(2,4,6-trimethylphenyl)ethane.

The great sensitivity of the formylation reaction to the reaction conditions can easily be seen from the fact that the yields of the aldehyde decrease significantly when the solvent is changed from high-boiling petroleum ether to low-boiling petroleum ether (Entries 8 and 9). The corresponding petroleum ether fractions influenced the velocity of the reaction in the same way in the Friedel–Crafts acylation reaction between naphthalene and acetyl chloride.[34]

The result of a Friedel–Crafts acylation reaction is also influenced by the nature of the Lewis acid used, and the same is true for the formylation of aromatic compounds with **9**. The yields of the aldehydes formed clearly depend on the Lewis acid acting as activator. In a few reactions we tried to find out whether aluminium chloride could be replaced by other Lewis acids. When *o*-xylene was formylated with tris(diformylamino)methane (**9**) and aluminium bromide (molar ratio 4:1:8) under the conditions given in Table 4, the 3,4-dimethylbenzaldehyde was obtained in 24% yield, whereas no formylation occurred even with a large excess of boron trifluoride–diethyl ether adduct (molar ratio 4:1:18). The replacement of aluminium chloride with boron trichloride in the formylation of *p*-cymene results in a decrease in the yield of aldehyde from 45 to 18%, while the formylation fails if boron tribromide or titanium tetrachloride is used as activator. From these results it is possible to deduce an order of the activating ability of Lewis acids for formylation of aromatic alkane compounds with tris(diformylamino)methane (**9**): $AlCl_3 > BCl_3 > BBr_3$. Unfortunately this order of activation power does not seem to be a general one, since no aldehyde was obtained in the attempted formylation of anisole with tris(diformylamino)-methane (**9**) and aluminium chloride under standard conditions (molar ratio 4:1:8, temperature $-13 \rightarrow -1$ °C/14 h). When, however, boron trichloride was used in reduced amounts (molar ratio 3:1:4) anisaldehyde was afforded in 20% yield.

Tris(diformylamino)methane (**9**) can also be activated by trifluoromethanesulfonic acid. Hence, 2,4-dimethoxybenzaldehyde was obtained in a yield of 84% from 1,3-dimethoxybenzene and tris(diformylamino)methane (**9**)/trifluoro-

Table 4. 3,4-Dimethylbenzaldehyde from *o*-xylene/tris(diformylamino)methane (**9**)/$AlCl_3$ (molar ratio 4:1:8) in various solvents

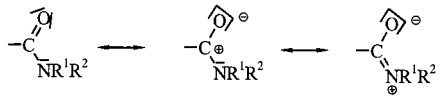
Entry	Solvent	Reaction conditions temp. [°C]/time [h]	Yield (%)
1	1,2-dichlorethane	$-13 \rightarrow -2/14$	65
2	nitromethane	$-10 \rightarrow +1/17$	0
3	nitrobenzene	$-10 \rightarrow -1/17$	0
4	SO_2 (liquid)	$-40 \rightarrow +10/16$	0
5	carbon disulfide	$-11 \rightarrow +2/17$	40
6	1,1,2-trichloro-trifluoroethane	$-10 \rightarrow +2/16$	17
7	chlorobenzene	$-9 \rightarrow +1/17$	31
8	petroleum ether (b.p. 110–140 °C)	$-11 \rightarrow +17/19$	23
9	petroleum ether (b.p. 40–80 °C)	$-9 \rightarrow +18/19$	10

methanesulfonic acid (molar ratio 1:9) in nitromethane at temperatures between −20 and 20 °C (2 h).

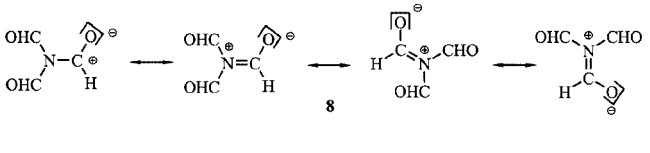
6. Formylation of Aromatic Compounds with *N*,*N*,*N*′,*N*′-Tetraformylhydrazine (12)[33,35]

The *N*,*N*,*N*′,*N*′-tetraformylhydrazine molecule has two adjacent nitrogen atoms, each of which bears two strongly electron-attracting formyl groups. As a consequence, the electrophilicity of the formyl groups should be enhanced in relation to those of diformamide (**6**) or tris(diformylamino)-methane (**9**) and might be expected to be similar to those of triformamide.

Usually, "amide resonance" reduces the electrophilicity of the carboxamide function, due to the importance of the resonance structure, in which the partial positive charge is localized at the nitrogen atom of the amide function.



It is very likely that resonance structures in which the positive charge is localized on the nitrogen atom contribute less to the structure of tetramethylhydrazine, since they lie energetically too high as a consequence of the close proximity of the two nitrogen atoms.



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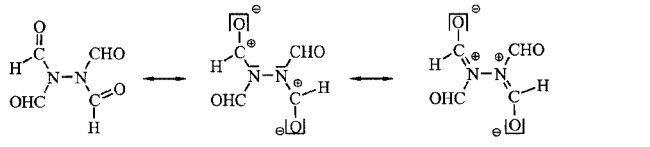


12

In the case of triformamide, resonance structures with a positive charge at the nitrogen atom may possibly contribute much more to the real structure, since the triformamide molecule is planar.[36]

In this context it is not very surprising that *N*,*N*,*N*′,*N*′-tetraformylhydrazine (**12**) turned out − after activation by aluminium chloride − to be a good formylation reagent for aromatic compounds such as heptylbenzene, *o*-xylene, mesitylene, naphthalene, anisole, and 1,3-dimethoxybenzene. The reactions between the aromatic compounds, *N*,*N*,*N*′,*N*′-tetraformylhydrazine (**12**) and aluminium chloride were run with a molar ratio of 4:1:4 in 1,2-dichloroethane or chlorobenzene. It seems that higher aldehyde yields are obtained when the reactions are performed at about room temperature. The primary reaction products from these formylation procedures are the corresponding aldazines **18**. Usually the reaction mixtures were worked up by steam distillation. During this process some of the aldazines are cleaved to give larger or smaller amounts of the free aromatic aldehyde, so the isolated products in some experiments were variously exclusively aldehydes, mixtures of aldehydes and aldazines, or exclusively aldazines. The results of some formylation reactions are given in Table 5.

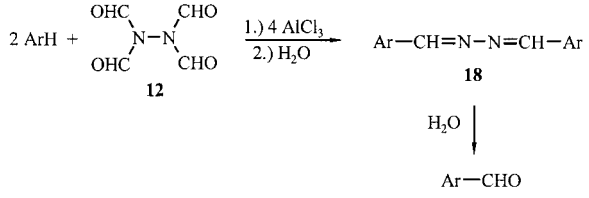
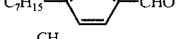
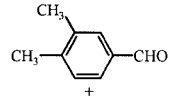
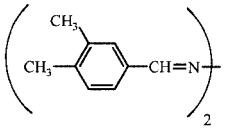
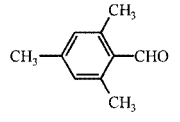
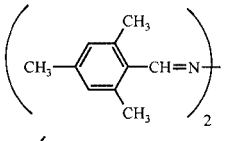
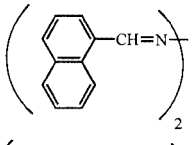
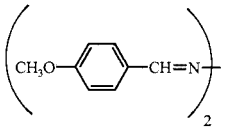
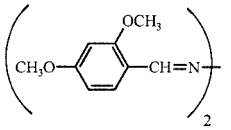


Table 5. Aromatic aldehydes from aromatic compounds/*N*,*N*,*N*′,*N*′-tetraformylhydrazine (**12**)/aluminium chloride (molar ratio 4:1:4)

Aromatic compound	Solvent	Reaction conditions temp. [°C]/time [h]	Products	Yield (%)[a]
heptylbenzene	A[b]	−3 → 0/14		64
o-xylene	B[c]	−11 → −1/19	 + 	9 77
mesitylene	B[c]	−11 → 0/18	 + 	21 68
naphthalene	A[b]	20/17		70[d]
anisole	B[c]	10 → 20/18		30[e]
1,3-dimethoxy-benzene	B[c]	0 → 13/19		72

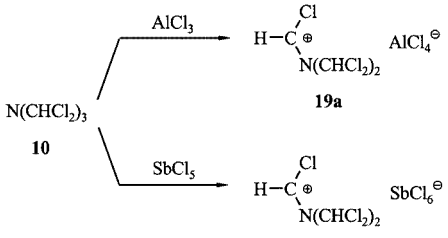
[a] Yields are calculated under the assumption that *N*,*N*,*N*′,*N*′-tetraformylhydrazine can deliver two formyl groups. [b] A = chlorobenzene. [c] B = 1,2-dichloroethane. [d] Isolated in two crops: 36% pure product, 34% product slightly contaminated with naphthalene. [e] Under milder reaction conditions [−1 → 12 °C (18 h)] the yield decreases to 10%.

Treatment of mesitylene with *N*,*N*,*N*′,*N*′-tetraformylhydrazine in the presence of trifluoromethanesulfonic acid (molar ratio 1:4) afforded 2,4,6-trimethylbenzaldehyde azine in a yield of 32%. When perfluorobutanesulfonic acid

was used for the activation of *N*,*N*,*N*′,*N*′-tetraformylhydrazine, 2,4,6-trimethylbenzaldehyde azine was produced in 32% yield, and 5% of 2,4,6-trimethylbenzaldehyde, derived from partial cleavage of the azine during the workup procedure, was also isolated.

7. Formylation of Aromatic Compounds with Tris(dichloromethyl)amine (10) in the Presence of Lewis Acids[33,38]

Triformamide is accessible by formolysis of tris(dichloromethyl)amine (**10**), but tris(dichloromethyl)amine (**10**) itself can be viewed as a formylating reagent in the presence of Lewis acid.[33,37] The compound is not ionised but is structurally closely related to the iminium chloride **1** used in Vilsmeier−Haack formylation reactions. The non-ionic (difluoromethyl)methylamine can be activated by Lewis acids; it ionises on addition of boron trifluoride.[38] The iminium salts **19a** and **19b** were similarly obtained from tris(dichloromethyl)amine and Lewis acids such as aluminium chloride and antimony pentachloride[39]



Salts of this type should have better formylation ability than adducts of the Vilsmeier−Haack type. In the cation of a Vilsmeier−Haack adduct, the positive charge is located predominantly at the nitrogen atom, whereas in a cation of the salts **19a** or **19b** the positive charge is preferentially centred at the carbon atom, as a consequence of the −*I*-effect of the dichloromethyl groups bound to the nitrogen atom.

Toluene cannot be formylated by the Vilsmeier−Haack reagents, so the above considerations might be verifiable by formylation reactions on toluene. Thus, tris(dichloromethyl)-amine (**10**) was treated with toluene in the presence of aluminium chloride and titanium tetrachloride. The results of these experiments are given in Table 6. Obviously, aluminium chloride is a better activator than titanium tetrachloride. To obtain sufficient yields of the aldehyde the molar ratio of tris(dichloromethyl)amine (**10**) and aluminium chloride should be about 1:4 or about 1:1 if titanium tetrachloride is used. In addition, the sequence in which the compounds are added also seems to be important. If the Lewis acid is added to the mixture of the aromatic compound and tris(dichloromethyl)amine (**10**), the aromatic aldehyde is isolated in significantly higher yields (compare Entries 3 and 4 in Table 6).

In some further experiments, the scope of the formylation reaction with tris(dichloromethyl)amine (**10**) in the presence of aluminium chloride and titanium tetrachloride was investigated. The results are given in Table 7.

The formylation ability of the tris(dichloromethyl)amine/aluminium chloride system is similar to that of the formyl fluoride/boron trifluoride system used in the Olah formylation reaction.[40] In Olah formylations of benzene and chlorobenzene the corresponding aldehydes are obtained in yields of 56 and 43%, respectively. Nearly the same yields of aldehyde are found if the tris(dichloromethyl)amine (**10**)/aluminium chloride system is used as formylating reagent.

As already observed in the reaction with triformamide, phenothiazine is formylated by tris(dichloromethyl)amine (**10**) at the nitrogen atom, to give 10-formylphenothiazine.

The following conclusions can be drawn from the formylation experiments with chlorobenzene: (i) at least under mild conditions, deactivated aromatic compounds are formylated by tris(dichloromethyl)amine only if a strong Lewis acid ($AlCl_3$) is used as activator, and (ii) the amounts of Lewis acid used in the formylation reaction can be reduced if higher reaction temperatures are chosen.

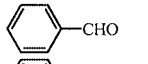
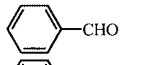
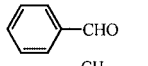
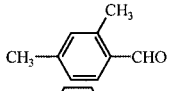
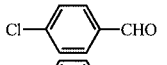
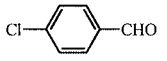
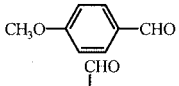
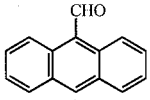
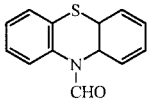
Activated aromatic compounds might therefore be formylated − possibly at higher temperatures − by tris(dichlo-

Table 6. *p*-Tolualdehyde from toluene and tris(dichloromethyl)amine (**10**) in the presence of aluminium chloride and titanium tetrachloride (reaction temperature: 0 → 20 °C, reaction time: 16 h)

Entry	Aromatic compounds	Molar amounts [mmol] and (molar ratio) of tris(dichloromethyl)amine/(Lewis acid)	Comments	Yield (%)
1	toluene[a]	22.6; 82.5 ($AlCl_3$) (1:3.6)		22
2	toluene[a]	56.4; 82.5 ($AlCl_3$) (2:3)	[b]	29
3	toluene[a]	22.6; 97.5 ($AlCl_3$) (1:4.3)	[b]	40
4	toluene[c]	22.2; 89.2 ($AlCl_3$) (1:4)	[d]	78
5	toluene[c]	19.6; 13 ($TiCl_4$) (1:0.7)	[d]	4
6	toluene[c]	19.9; 48.5 ($TiCl_4$) (1:2.4)	[d]	25
7	toluene[c]	21.1; 30.0 ($TiCl_4$) (1:1.4)	[d]	47
8	toluene[c]	15.8; 16.3 ($TiCl_4$) (1:1)	[d]	52.6

[a] Toluene (50 mL) was both the substrate and the solvent. [b] Tris(dichloromethyl)amine was added to the mixture of the aromatic compound and the Lewis acid. [c] Toluene (25 mL) was both the substrate and the solvent. [d] The Lewis acid was added to the mixture of toluene and tris(dichloromethyl)amine.

Table 7. Aromatic aldehydes from aromatic compounds and tris(dichloromethyl)amine (**10**) and aluminium chloride and titanium tetrachloride

Entry	Aromatic compounds	Molar amounts [mmol] and {molar ratio} of tris(dichloromethyl)amine/(Lewis acid)	Reaction conditions	Product	Yield (%)	Comments
1	benzene[a]	27.8; 82.5 ($AlCl_3$) {1:3}	[b]		13.5	[c]
2	benzene[d]	19.6; 84.8 ($AlCl_3$) {1:4.3}	[b]		57.5	[e]
3	benzene[d]	21.8; 44.2 ($TiCl_4$) {1:2}	[e]		13	[f]
4	*m*-xylene[c]	20.3; 31.1 ($TiCl_4$) {1:1.5}	[b]		36	[f]
5	chlorobenzene[d]	19.9; 82.5 ($AlCl_3$) {1:4.1}	[b]		29	[e]
6	chlorobenzene[g]	5.0; 6.0 ($AlCl_3$) {1:1.2}	[h]		32	[e]
7	chlorobenzene[g]	5.0; 6.0 ($AlCl_3$) {1:1.2}	[i]	...	0	[e]
8	chlorobenzene[d]	21.1; 25.8 ($TiCl_4$) {1:1.2}	[b]	...	0	[f]
9	anisole[d]	21.4; 31.1 ($TiCl_4$) {1:1.5}	[b]		34	[f]
10	anthracene[j]	13.2; 6.3 ($TiCl_4$) {2:1}	[b]		48	[f]
11	phenothiazine[k]	7.9; 22.2 ($TiCl_4$) {1:2.8}	[i]		66	[f]

[a] The aromatic compound (50 mL) was both the substrate and the solvent. [b] Reaction temperature 0 → 16 °C, reaction time 16 h. [c] The tris(dichloromethyl)amine (**10**) was added to the mixture of the aromatic compound and the Lewis acid. [d] The aromatic compound (25 mL) was both the substrate and the solvent. [e] Reaction temperature 0 → 20 °C, reaction time 72 h. [f] The Lewis acid was added to the mixture of the aromatic compound and tris(dichloromethyl)amine (**10**). [g] The aromatic compound (10 mL) was both the substrate and the solvent. [h] Reaction temperature 0 → 60 °C, reaction time 18 h. [i] Reaction temperature 0 → 20 °C, reaction time 30 h. [j] 40.4 mmol dissolved in 25 mL of chlorobenzene. [k] 31.6 mmol dissolved in 25 mL of chlorobenzene. [l] Reaction temperature 0 → 20 °C, reaction time 24 h.

romethyl)amine (**10**) in the presence of smaller amounts of weaker Lewis acids. Experiments on the formylation of anisole with tris(dichloromethyl)amine (**10**) and zinc chloride as activator seem to confirm this supposition. The results of these investigations are given in Table 8.

Table 8. Anisaldehyde from anisole and tris(dichloromethyl)amine (**10**)/zinc chloride under various reaction conditions

Molar ratio[a] of tris(dichloromethyl)-amine/zinc chloride	Reaction conditions temp. [°C]/time [h]	Yield (%)[b]	*o*/*p* ratio[c]
1:1	0/1 and 20/18	21	1:9
1:2	0/1 and 20/18	28	1:11.5
1:3	0/1 and 20/18	21	1:8
1:0.12	60−65/3	6.2	1:19
1:1	60−65/3	56	1:19
1:2	50−60/3	62.5	1:24
1:3	60−65/3 and 20/18	63	1:19

[a] In these experiments, 15.8 mmol of tris(dichloromethyl)amine (**10**) and 20 mL of anisole were used. [b] The products were mixtures of *o*- and *p*-methoxybenzaldehyde; yields are calculated on the assumption that tris(dichloromethyl)amine provides one formyl group. [c] Determined by gas chromatography.

Use of the aromatic compound as the solvent will not always make sense, in cases of expensive compounds, for example, or those available only in low quantities, it is desirable to know some solvents in which the formylation reactions can be performed. To close this gap in our knowledge, the formylation of anisole with tris(dichloromethyl)amine (**10**)/zinc chloride in a range of solvents was studied. The results are given in Table 9.

From these results it can be concluded that polar solvents of low Lewis basicity, such as nitroalkanes, acetonitrile, phosphoryl chloride and methanesulfonyl chloride, are best suited for the formylation of aromatic compounds with tris(dichloromethyl)amine (**10**).

The activation of tris(dichloromethyl)amine (**10**) by protonation was studied in more detail.[41] On treatment of toluene with tris(dichloromethyl)amine (**10**) and fluorosulfonic acid (molar ratio 1:2) a mixture of *o*- and *p*-tolualdehyde (1:30) is obtained in 24% yield. The aldehyde yields decrease if the molar ratio in the formylation system is changed (1:1 or 1:4, yield only 15%). Mixtures of fluorosulfonic acid/antimony pentafluoride (1:1) and tris(dichloromethyl)amine (**10**) (1:1) react with toluene to give mixtures of all regioisomeric tolualdehydes (*o*/*m*/*p* = 5:1:25) in a yield of 19%. A similar mixture of tolualdehydes (1:0.15:9)

Table 9. Anisaldehyde from anisole and tris(dichloromethyl)amine (**10**)/zinc chloride (molar ratio 1:1:1.25) in various solvents; temp. 60−65 °C, time 3 h

Solvent	Yield (%)	*o*/*p* ratio
Tetrachloromethane	3.6	1:23
Hexane	2.8	1:16.5
Benzene	6.1	1:5.6
Nitrobenzene	13.1	1:5.9
Nitromethane	24	1:5.7
Nitroethane	22	1:5
2-Nitropropane	16	1:5
Chloroform	4	1:11
Acetonitrile	18	1:7
Phosphoryl chloride	26	1:4
Methanesulfonyl chloride	22.5	not determined
Hexamethyldisiloxane	6	1:6
Pyridine	0	−
N,*N*,*N*′,*N*′-Tetramethylurea	0	−

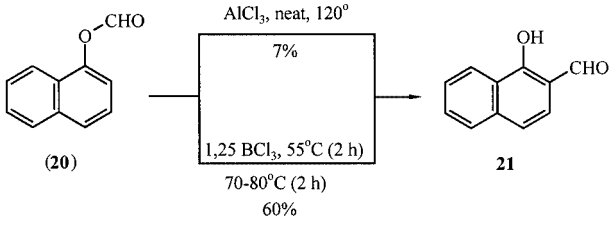
can be prepared in 51% yield by treatment of toluene with tris(dichloromethyl)amine (**10**)/perfluorobutanesulfonic acid (1:2) at 0 °C. When trifluoromethanesulfonic acid was used to activate tris(dichloromethyl)amine (**10**) it turned out that a mixture in a molar ratio of 2.5:1 was most effective; in the reaction with toluene a mixture of *o*- and *p*-tolualdehyde (1:10) was produced in 71% yield. A similar mixture (*o*/*p* = 1:8) of tolualdehydes was afforded in 56% yield by the action of a mixture of trifluoromethanesulfonic acid/antimony pentafluoride (8:1) and tris(dichloromethyl)amine (1:1) on toluene. Anisole could be formylated with tris(dichloromethyl)amine (**10**)/trifluoromethanesulfonic acid (1:1.2) at −30 °C to give a mixture of *o*- and *p*-methoxybenzaldehyde (1:6) in a yield of 50%. The corresponding triarylmethanes were by-products in all acid-catalysed aldehyde syntheses with tris(dichloromethyl)amine (**10**).

8. Aromatic Hydroxyaldehydes from Aryl Formates by Means of Fries Rearrangements[42]

For the formylation of hydroxyarenes, only a few methods affording the corresponding hydroxyarenecarbaldehydes in acceptable yields are known. Thus, simple hydroxyarenes can be formylated with dichloromethyl methyl ether/titanium tetrachloride (Groß−Rieche formylation), with hydrocyanic acid/hydrogen chloride/$AlCl_3$ (Gattermann formylation), and with chloroform/sodium hydroxide (Reimer−Tiemann reaction). Di- and trihydroxybenzenes are transformed into the corresponding aromatic aldehydes on treatment with methyl orthoformate/$AlCl_3$,[43] while the Vilsmeier−Haack reagent is less suited for such purposes. A standard method for the preparation of hydroxyaromatic ketones is the Fries reaction, in which aryl esters of carboxylic acids are rearranged in the presence of Lewis acids or superacids to give hydroxyaromatic ketones. According to this procedure, hydroxyaromatic aldehydes should be accessible from aryl formates, but it can be stated on the basis of rearrangement experiments with phenyl formate that the Fries rearrangement is not a suitable method for the preparation of hydroxyaromatic aldehydes.[3c]

Acylium ions are very likely − or even proven, at least in the case of the super acid induced reactions − intermediates in the Fries rearrangement.[44] The Fries rearrangement may fail if conditions giving rise to the formation of formylium ions are chosen. The observation that aluminium chloride decomposes formyl fluoride, whereas adducts from formyl fluoride and boron halides are fairly stable, can be taken as a hint in this direction.[3c]

By this hypothesis, Fries rearrangements with aryl formates might be possible (if possible at all), provided that the proper conditions, especially the appropriate Lewis acids, were chosen. When 1-naphthyl formate (**20**) was heated with molar amounts of aluminium chloride, 1-hydroxy-2-naphthaldehyde (**21**) was obtained in a yield of 7%. The same aldehyde was isolated in a yield of 60% from 1-naphthyl formate and boron trichloride in 1,2-dichloroethane.

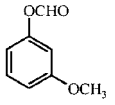
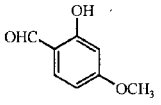
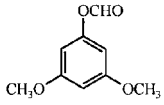
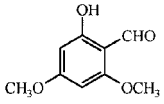
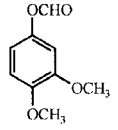
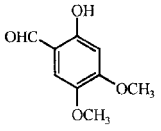
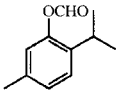
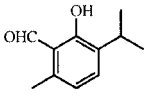
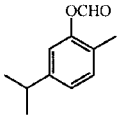
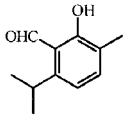
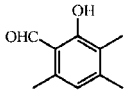
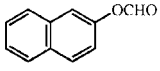
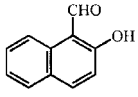
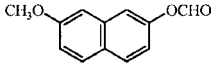
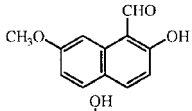
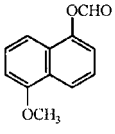
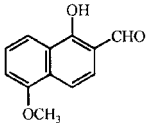
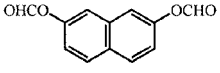
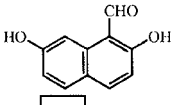
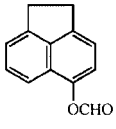
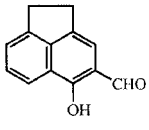
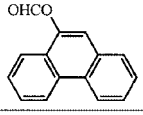
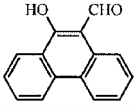


These experiments showed that the Fries rearrangement with aryl formates was in principle possible, and a lot of aryl formates have been rearranged to the corresponding hydroxyaromatic aldehydes with the aid of boron halides. The results are given in Table 10.

The results from Table 10 show that the Fries rearrangement of formyl groups is strongly influenced by the Lewis acid used. Boron tribromide is more effective than boron trichloride (Entries 1 and 2). One striking observation is that, in a case in which only small aldehyde yields were obtained under standard conditions, the use of a mixture of Lewis acids (BBr_3 + $FeCl_3$) was able to improve the yield dramatically (Entries 7 and 11). The combination of Lewis acids is of little effect if the rearrangement already occurs with sufficient yield with a boron halide as activator (Entries 14, 15). From the experiments (Entries 5−11) it can be inferred that chlorobenzene and carbon disulfide are the most advantageous solvents for Fries rearrangements of formyl groups.

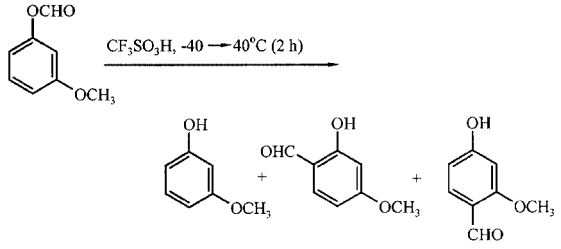
Fries rearrangements of formyl groups can also be induced by trifluoromethanesulfonic acid. Interestingly, different regioisomeric aldehydes are also formed, as in the boron trihalide catalysed reaction. The rearrangement is accompanied by decarbonylation of the aryl formate or of the formed aldehyde. When 3-methoxyphenyl formate was treated with trifluoromethanesulfonic acid, a mixture of 3-methoxyphenol (50%), 2-hydroxy-4-methoxybenzaldehyde

Table 10. Hydroxyaromatic aldehydes obtained by boron halide induced Fries rearrangement of aryl formates

Entry	Aryl formate	Amount of activator [mol] (solvent)	Reaction conditions temp. [°C] (time [h])	Product	Yield (%)
1		1.2 BCl_3 (1,2-DCE)[a]	−20 → 30 (0.5)		27
2		1.2 BBr_3 (1,2-DCE)	−10 → 20 (20)		59
3		1.2 BCl_3 (1,2-DCE)	5 → 20 (2)		94
4		1.2 BBr_3 (1,2-DCE)	−14 → 15 (2)		72
5		1.0 BBr_3[b] (1,2-DCE)	20 (20)		traces[c]
6		hexane[b]	20 (20)		–
7		chlorobenzene[b]	20 (20)		7.4[d]
8		carbon disulfide[b]	20 (20)		13[4]
9		carbon disulfide[b]	20 (48)		7[d]
10		carbon disulfide[b]	20 (72)		4[d]
11		1.12 BBr_3 + 1.12 $FeCl_3$ (chlorobenzene)	−15 → 12 (20) 20 (0.5)		70[d]
12		1.12 BBr_3 + 1.12 $FeCl_3$ (chlorobenzene)	−15 → 12 (20)		58
13		1.0 BBr_3 + 1.0 $FeCl_3$ (chlorobenzene)	−15 → 20 (3)		55
14		1.05 BBr_3 + 1.0 $FeCl_3$ (chlorobenzene)	−15 → 15 (20)		64
15		1.05 BBr_3 (chlorobenzene)	−15 → 15 (20)		61
16		1.2 BCl_3 (hexane)	25 (96)		53
		1.2 BCl_3 (1,2-DCE)	20 → 75 (1.5)		71
17		1.5 BCl_3 (1,2-DCE)	5 → 20 (2)		57
18		1.1 BCl_3 (1,2-DCE)	0–5 (1); 20 (2)		40
19		2.1 BBr_3 (1,2-DCE)	0–5 (2.5)		56
20		1.2 BCl_3 (1,2-DCE)	20 → 55 (2)		66
21		1.2 BCl_3 (1,2-DCE)	20 → 35 (2)		98

[a] 1,2-DCE = 1,2-dichloroethane. [b] Several solvents and different reaction conditions were tested in the rearrangement of 2-isopropyl-5-methylphenyl formate − in all experiments (Entries 5−10) 1 mol of BBr_3 was used, in two experiments (Entries 10 and 11) mixtures of 1.12 mol of BBr_3 and 1.12 mol of $FeCl_3$were used. [c] Positive test with 2,4-dinitrophenylhydrazine. [d] Yields determined by ^1H NMR spectroscopy.

(25%), and 4-hydroxy-2-methoxybenzaldehyde (25%) was obtained.

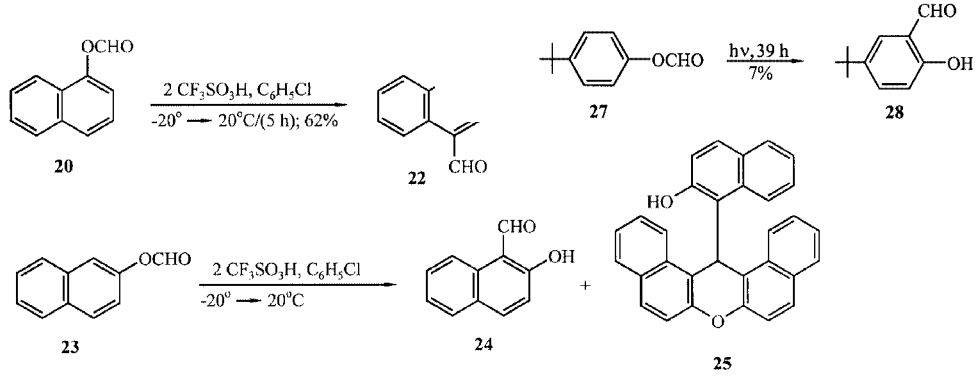


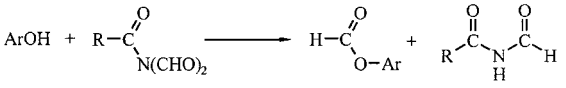
Similarly, 1-naphthyl formate (**20**) rearranged to give 4-hydroxy-1-naphthaldehyde (**22**) in 62% yield, whereas the rearrangement of 2-naphthyl formate (**23**) afforded 2-hydroxy-1-naphthaldehyde (**24**) in 18% yield. In the latter reaction, the xanthene derivative **25** was also isolated, in 40% yield. The formation of this compound shows that the aldehyde yields can be reduced by subsequent reactions of the formed aldehyde with the hydroxyarene produced by decarbonylation of the aryl formate. Such side-reactions have also been suspected to occur in attempted formylations of phenols by the Gattermann−Koch method.[3c]

The aryl formates needed for the Fries rearrangement can be prepared in a fairly general method from the corresponding hydroxyarenes and triformamide **8** or *N*,*N*-diformylacetamide **7**.[45]

The following mechanism has been proposed for the Fries rearrangement of formyl groups in the presence of boron halides. In the primary adduct originating from the aryl formate and the boron halide, a halide ion is transferred from the boron atom to the positive carbon atom, giving rise to the formation of an ester of dichloroboric acid. As a consequence of the change in coordination at the boron atom, an electrophile **26** is generated from the ester, and this can attack the aromatic compound in a six-centred transition state. An analogous mechanism may compete with the acylium ion pathway in the classical Fries rearrangement.

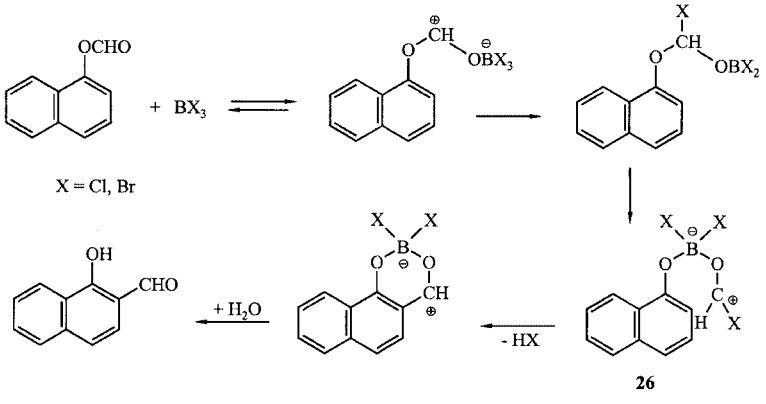
The Fries reaction can also be performed photochemically, the rearrangement of a formyl group under such conditions having been observed in one case. When 4-*tert*-butylphenyl formate (**27**) was irradiated for 39 h in benzene, 5-*tert*-butyl-2-hydroxybenzaldehyde (**28**) could be isolated in 7% yield.[46]

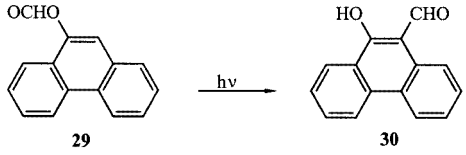




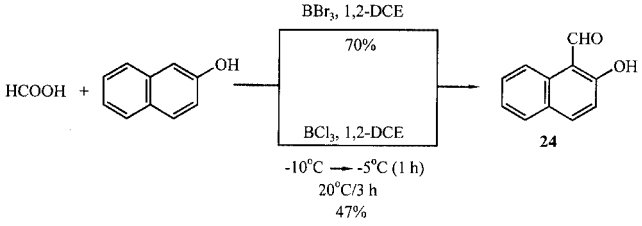
7 : R = CH_3
8 : R = H

The photochemical procedure may have high synthetic potential, since it has been noted that 9-phenanthrenyl formate (**29**) is rearranged to 10-hydroxyphenanthrene-9-carbaldehyde (**30**) on standing in sunlight.[42]





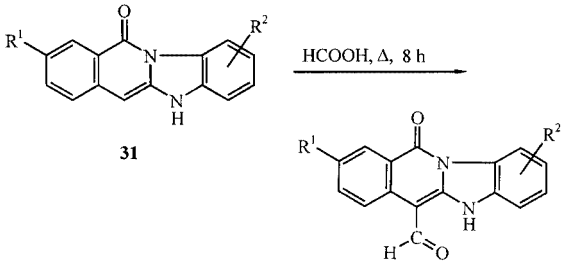
29 30



24

9. Formylation of Aromatic Compounds with Formic Acid or Formamide in the Presence of Lewis Acids

Alkoxyarenes, hydroxyarenes and aromatic alkane compounds can be substituted at the aromatic nucleus with carboxylic acids in the presence of various Lewis acids, and also with perchloric acid or polyphosphoric acid.[47] Such reactions have been also performed with methanesulfonic acid[48] or trifluoromethanesulfonic acid.[49] Carboxylic acids of great structural variety were used in these reactions. Curiously, there are only a few reports dealing with the formylation of aromatic compounds by formic acid. In the reaction between formic acid and chlorobenzene in the presence of 2.5 mol-equiv. aluminium chloride, resinous products are mainly formed, but in addition, up to 2% of *p*-chlorobenzaldehyde was also isolated.[50] The formylation of toluene by formic acid in trifluoromethanesulfonic acid was investigated in a kinetic study, in which a mixture of *o*- and *p*-tolualdehyde (*o*/*p* = 1:15.6) was obtained in a yield of 7.4% (GC).[49] Benzimidazoisoquinolines **31** contain highly reactive ketene N,N-acetal structures, allowing the formylation of these compounds by simple heating with formic acid.[51]



31

The naphthol derivative **32** is transformed into the oxonium salt **33** on treatment with formic acid/polyphosphoric acid.[52]

In the Fries reaction of aryl formates, intermediates such as **26** were considered.[42] Compounds of this type should be formed if mixtures of formic acid and hyroxyarenes are treated with boron halides. In accordance with this assumption, 2-hydroxy-1-naphthaldehyde (**24**) was obtained in a yield of 70% from formic acid, 2-naphthol, and boron tribromide in 1,2-dichloroethane.[42] The same aldehyde was obtained in about 47% yield if boron trichloride was used instead of boron tribromide.[53]

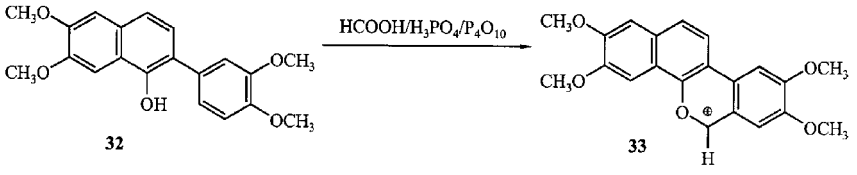
The formylation of 1,3-dimethoxybenzene with formic acid was studied in greater detail.[54] To obtain acceptable yields (33%) of 2,4-dimethoxybenzaldehyde, dimethoxybenzene, boron trichloride, and formic acid should be allowed to react in a molar ratio of about 1:2:1.1 at temperatures from −15 to −10 °C in 1,2-dichloroethane for 1−5 h. Surprisingly, the yield could be significantly improved if a mixture of heptane and 1,2-dichloroethane was used as solvent.

In a preliminary study,[54] it was shown that 2-methylanisole, 3-methylanisole, 1,3-diethoxybenzene, 3-methoxyphenol, anisole, and 2-ethoxynaphthalene are formylated by formic acid/BCl_3 in dichloromethane or 1,2-dichloroethane at −15 to −10 °C within about 2 h, giving aldehydes in yields of about 20%. In these investigations the reaction mixtures were hydrolysed, the organic liquids were separated and dried, and the solvent was removed. The aldehyde contents in the residues were determined by ^{1}H NMR spectroscopy. Since the aldehydes were not isolated in the pure state, it is not certain at present whether this formylation procedure will acquire practical significance.

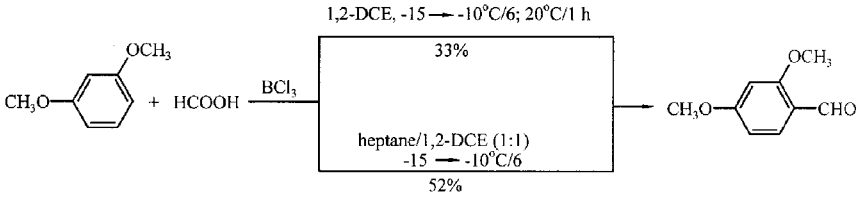
The main products in the formylation reactions in the presence of formic acid and boron trichloride are very often triarylmethane derivatives, together with higher, unidentified condensation products. The formation of the triarylmethanes indicates the formation of the aromatic aldehyde in the first step of the reaction. Under the applied reaction conditions, however, further condensation occurs, giving triarylmethanes and higher condensation products.

Formic acid and phosphorus pentoxide were assumed to form labile mixed anhydrides which should be capable of formylating aromatic compounds on activation with aluminium chloride. When toluene was treated with such mixtures, tolualdehydes were obtained in less reproducible reactions in small yields. Carbon monoxide is evolved in these reactions, indicating the low stabilities of mixed anhydrides of formic acid and the oligophosphorous acids.

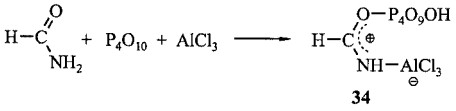
Better formylation results were obtained with mixtures of formamide, phosphorus pentoxide, and aluminium chloride. In first experiments with this formylation system, tolualdehyde and anisaldehyde were obtained from toluene and anisole in yields of 9 and 15%, respectively.[26] Adducts **34** from aluminium chloride and mixed anhydrides from for-



32 33



mimidic acid and oligophosphorous acids are thought to be the reactive intermediates.



10. Conclusion

This article has shown that oligoformylamines and tris(-dichloromethyl)amine can be used as formylating reagents for aromatic compounds. Furthermore, it has been reported that aromatic hydroxyaldehydes can be prepared by means of Fries rearrangement of aryl formates.

Methodical improvements should surely result if other organic chemists use and vary these new formylation procedures. It is very likely that other − hitherto unknown − oligoformylamines also suitable to serve as formylating reagents may be prepared. Additionally, considerable investigation will be necessary to find out the exact formylation mechanisms with the new reagents. It may also be expected that the oligoformylamines should find application beyond aromatic substitution processes.

Acknowledgments

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