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N-ALKYLATION OF NITRILES—I
A GENERAL SYNTHESIS OF SUBSTITUTED AMIDINES

R. FUKS*
Union Carbide European Research Associates, rue Gatti de Gamond 95
B-1180 Brussels Belgium

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Abstract—A general synthesis of substituted amidines has been worked out starting from a nitrile compound, an alkyl halide, a Lewis acid and an amine.

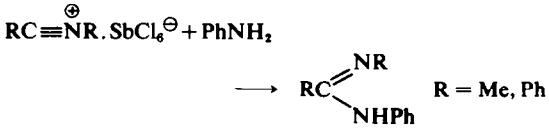
The method involves 4 steps:

(1) formation of a nitrile–Lewis acid complex **2**;
(2) N-Alkylation of this complex **2** with an alkyl halide and formation of a nitrilium salt **3**;
(3) aminolysis of the nitrilium salt **3** with ammonia, a primary or a secondary aliphatic or aromatic amine to get the amidinium salt **4**;
(4) neutralization of the amidinium salt with a base yielding the substituted amidine **5**.

In practice, the amidine **5** is obtained in a one-pot synthesis and none of the intermediates **2**, **3** or **4** needs to be isolated. Overall yields of 40–80% based on the nitrile **1** are obtained. More than twenty new mono-, di or trisubstituted amidines have been prepared by this procedure.

INTRODUCTION

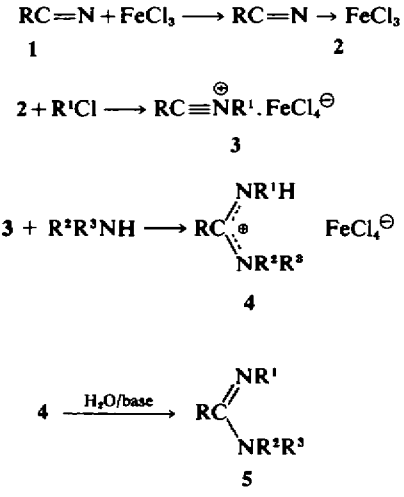
It is well known that nitriles complexed with Lewis acids react with alkyl halides to form nitrilium salts.[1] There is little known about their chemistry, although they have already been isolated and characterized in 1955.[2,3] They are strong electrophiles, and easily converted to amides with water,[2] to imidates with alcohol,[4,5] to amidines with amines,[5] and to tetrazole with sodium azide.[6] So far the formation of amidines has, however, been carried out only in the two following examples with the intention to characterize the nitrilium function:[5]



In view of the interest of amidines[7] and the fact that there are only a few methods to prepare N,N'-substituted amidines, we have studied the generality of this reaction as a convenient preparative method for the synthesis of mono-, di- or trisubstituted amidines via the following steps: (a) N-alkylation of a nitrile–Lewis acid complex[30] by the Meerwein's method[2] with an alkyl halide to from the corresponding nitrilium salt. (b) Aminolysis with an amine and isolation of the amidine via its salt.

RESULTS

Acetonitrile and benzonitrile (**1**) have been used resp. as typical aliphatic and aromatic nitriles.



Ferric chloride has been chosen as one of the most common and effective Lewis acids in the formation of the nitrilium salt **3**. The N-alkylation of the complex **2** with t-butyl chloride was completed within 30 min, whereas with isopropyl chloride it took a few hours.[2] The aminolysis of **3** with ammonia, a primary or a secondary aliphatic or aromatic amine was very exothermic. All steps were carried out between −10° and room temperature. It was not necessary to isolate the intermediates **2**, **3** or **4**. The overall yields of this one-pot synthesis ranged from 60–80% when isopropyl chloride was used in the N-alkylation and from 30–50% yield with t-butyl chloride (Table 1).

The nitrilium salt **3** with R^1 = t-butyl seems to

*New address: Université Libre de Bruxelles, Chimie Générale I, 50, Av. Franklin Roosevelt, B-1050 Bruxelles.

Table 1. Overall yields in N-substituted amidines 5 obtained from the nitriles 1

5. N°	R	R^1	R^2	R^3	m.p. (°C) b.p. (°C/Torr)	Yield %
1	Me	$CHMe_2$	$(CH_2)_5$		95–100/0·1	78
2	Me	$CHMe_2$	H	Ph	86	57–67
3	Me	$CHMe_2$	H	C_6H_4-*p*Cl	87	71
4	Me	$CHMe_2$	H	C_6H_3-*m.p.* diCl	94	70
5	Me	$CHMe_2$	H	C_6H_3-*o*Me-*p*Cl	120	62–70
6	Me	$CHMe_2$	H	C_6H_4-*p*OMe	97	60
7	Me	$CHMe_2$	H	C_6H_4-*m*OH	156	20–30
8	Me	$CHMe_2$	H	H	25–34	30
9	Ph	$CHMe_2$	Et	Et	100/0·1	80
10	Ph	$CHMe_2$	$(CH_2)_5$		160/12	70
11	Ph	$CHMe_2$	H	Ph	87	77
12	Me	CMe_3	Et	Et	80/12	34
13	Me	CMe_3	$(CH_2)_4$		110/17	30
14	Me	CMe_3	$(CH_2)_5$		110–115/12	40
15	Me	CMe_3	$(CH_2)_2O(CH_2)_2$		118/19	38
16	Me	CMe_3	H	H	72–74	30
17	Me	CMe_3	H	Ph	138/16	37
18	Me	CMe_3	H	C_6H_4-*p*Cl	160/16	40
19	Me	CMe_3	H	C_6H_3-*o*Me-*p*Cl	104/0·1	53–65
20	Me	CMe_3	H	C_6H_4-*o*COOMe	54–55	50
21	Ph	CMe_3	Et	Et	90/0·1	52
22	Ph	CMe_3	$(CH_2)_5$		30–31	50

be unstable under basic conditions since already at the beginning of the aminolysis the reaction mixture becomes dark, whereas with R^1 = isopropyl it remains clean (yellow–brown) during the whole addition of the amine.

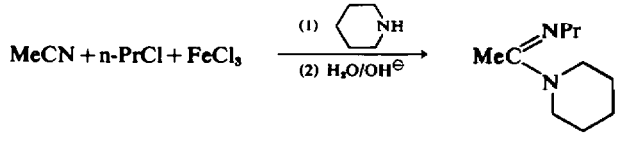
The nitriles 1 (R = CH_3 or C_6H_5) form with ferric chloride 1:1- and 2:1-adducts.[3b] To reach the optimum yield of Table 1 it is, however, necessary to pass via the 1:1-adduct. In one experiment, in which half of the ferric chloride was used (considering a 2:1-adduct of nitrile-ferric chloride) only half of the yield in amidine was obtained.

The nitrilium salt 3 can be isolated,[2] and e.g. the aminolysis of 3 (R = CH_3, R^1 = $CHMe_2$) with piperidine provided pure N-isopropyl-N′N′-pentamethylene acetamidine 5 R = Me; R^1 = $CHMe_2$; R^2R^3 = $(CH_2)_5$ in 88% yield. This means that the nitrilium salt may be prepared independently by any other method[1–5] in order to carry out its aminolysis to the amidine.

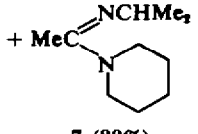
As it was to be expected, attempts to prepare the N-propylamidine derivative via N-alkylation with propyl chloride gave 43% yield of a mixture containing 80% of the N-isopropyl amidine (7) and only 20% of the N-propyl amidine (6), estimated by NMR.

The N-alkylation with n-butyl chloride afforded 25% pure N-sec-butyl derivative 8. Attempts to prepare the same amidine 8 with sec-butyl chloride led to its decomposition under the reaction conditions (steam bath temp).

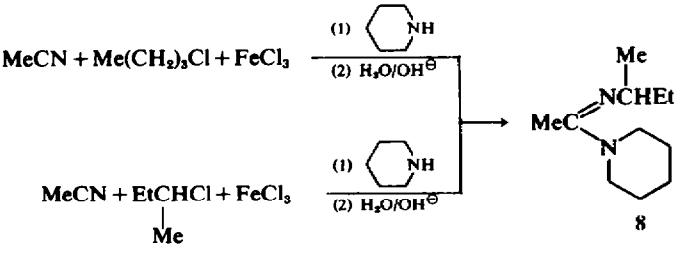
A dialkylation has been carried out with adiponitrile. The dinitrilium salt 9 was identified by its hydrolysis to bis N-isopropyladipamide 10.



6 (20%)



7 (80%)



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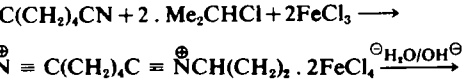

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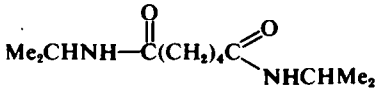

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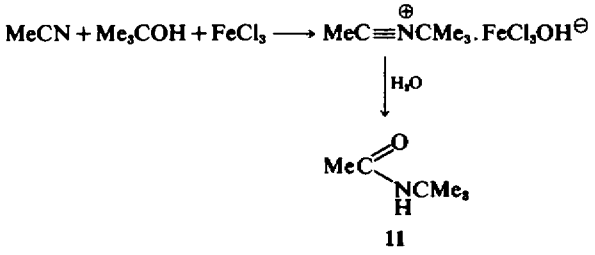
The reaction of t-butyl alcohol with a nitrile in the presence of BF_3 gives the amide **11** in good yield.[8] We have obtained similar results with ferric chloride as the Lewis acid in much lower yield however.



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CONCLUSION

The number of examples (Table 1) of aliphatic or aromatic mono-, di- or tri-substituted amidines containing aliphatic, cycloaliphatic or aromatic substituents show the generality of the method. The very mild reaction conditions make this process particularly useful for the synthesis of thermal sensitive amidines. This will be demonstrated in the next paper of this series in which N-substituted acrylamidines have been prepared for the first time by this method.

EXPERIMENTAL

Technical assistance of Mr. M. A. Hartemink and Mrs. E. Szalai. M.ps and b.ps are uncorrected. IR spectra were taken as KBr pellets with a Perkin-Elmer model 21 double-beam instrument, NMR spectra on a Varian A-60 instrument, using TMS as an internal standard. Analytical data are given in Table 2. Elemental analyses carried out by Mr. F. Goes of this laboratory.

General method for acetamidines with isopropyl chloride (5 No. 1 to 8 of Tables 1 and 2). A suspension containing $FeCl_3$ (16·4 g; 0·101 M) in 40 ml i-PrCl and MeCN (4·5 g; 0·101 M) kept at 0° for 3 hr. The excess of *i*-PrCl was evaporated to dryness and 3 was taken up in 20 ml CH_2Cl_2, and the amine (0·095 M) in 10 to 50 ml CH_2Cl_2 was added dropwise to the suspension. The mixture was kept 2 hr at room temp. The CH_2Cl_2 was then evaporated to dryness and the residue, salt 4 was taken up in water. To the mixture at 0° 30% NaOH (4·5 mole equiv) was added and the mixture extracted with ether. The ethereal extracts were dried, concentrated and distilled in a 3-bulb tube under high vacuum. The b.ps or m.ps are indicated in Table 1 and analytical data in Table 2. The amidines 5 No. 2, 3 and 4 were crystallized from light petroleum 40–60; No. 5 and 6 from a mixture of ether–light petroleum 40–60 and No. 7 from MeOH.

General method for benzamidines with isopropyl chloride (5 No. 9, 10 and 11 cf. Tables 1 and 2). N-Isopropyl-benzonitrilium tetrachloroferrate was prepared following the method described by Meerwein[2] and the aminolysis was as above in ether as solvent. The amidine No. 11 was recrystallized from ether.

General method for acetamidines with t-butyl chloride (5 No. 12 to 20 *cf* Tables 1 and 2). To $FeCl_3$ (23·1 g; 0·145 M) in 40 ml CH_2Cl_2 at 0° MeCN (5·85 g; 0·145 M) was added. After 15 min, t-BuCl (13·4 g; 0·145 M) was added and the mixture kept 30 min at 0°, during which time the salt 3 was formed. Then the amine (0·136 M) in 10 to 100 ml CH_2Cl_2, depending on the solubility, was added dropwise to the mixture (temp below 0° for 1 to 2 hr). The solvent was then evaporated to dryness, the residue 4 was taken up in water and 30% NaOH (4·5 moles equiv) was added under ice water cooling. The amidine 5 was then extracted with ether. The organic extracts were dried, concentrated and distilled in a 3-bulb tube under high vacuum. The compounds No. 16 and 20 were recrystallized from pentane.

General method for benzamidines with t-butyl chloride (5 No. 21 and 22). N-t-butyl-benzonitrilium tetrachloroferrate was prepared from benzonitrile and t-BuCl following the method described by Meerwein.[2] The aminolysis was carried out directly in CCl_4 as solvent by adding the

Table 2. Elementary analyses of the N-substituted amidines, 5

5. N°	Formula	M.W.	Calculated C	H	N	O	Cl	Found C	H	N	O	Cl
1	$C_{10}H_{20}N_2$	168	71·37	11·98	16·65	—	—	69·91	12·27	16·60	—	—
2	$C_{11}H_{16}N_2$	176	74·96	9·15	15·89	—	—	74·95	9·20	16·03	—	—
3	$C_{11}H_{15}ClN_2$	210	62·7	7·13	13·28	—	16·85	62·79	7·30	13·42	—	17·00
4	$C_{11}H_{14}Cl_2N_2$	245	53·8	5·72	11·42	—	29·00	54·10	5·93	11·84	—	29·22
5	$C_{12}H_{17}N_2Cl$	224	64·2	7·57	12·46	—	15·80	64·13	7·41	12·20	—	15·70
6	$C_{12}H_{18}N_2O$	206	69·87	8·80	13·58	7·76	—	69·73	8·86	13·63	7·82	—
7	$C_{11}H_{16}N_2O$	192	68·72	8·39	14·57	8·32	—	68·42	8·26	14·50	—	—
8	$C_5H_{12}N_2$*	100	59·96	12·08	27·97	—	—	—	—	—	—	—
9	$C_{14}H_{22}N_2$	218	77·01	10·16	12·83	—	—	76·85	10·28	12·72	—	—
10	$C_{15}H_{22}N_2$	230	78·21	9·63	12·16	—	—	78·20	9·40	12·26	—	—
11	$C_{16}H_{18}N_2$	238	80·63	7·61	11·75	—	—	80·72	7·69	11·75	—	—
12	$C_{10}H_{22}N_2$	170	70·53	13·02	16·45	—	—	70·72	13·36	16·53	—	—
13	$C_{10}H_{20}N_2$	168	71·37	11·98	16·65	—	—	70·89	12·07	16·67	—	—
14	$C_{11}H_{22}N_2$	182	72·47	12·16	15·37	—	—	71·89	12·14	14·99	—	—
15	$C_{10}H_{20}N_2O$	184	65·17	10·94	15·20	8·68	—	65·23	10·81	15·27	9·01	—
16	$C_6H_{14}N_2$*	114	63·11	12·36	24·53	—	—	—	—	—	—	—
17	$C_{12}H_{18}N_2$	190	75·74	9·54	14·72	—	—	75·39	9·76	15·22	—	—
18	$C_{12}H_{17}N_2Cl$	260	64·2	7·57	12·46	—	15·8	64·58	7·76	12·30	—	15·67
19	$C_{13}H_{19}N_2Cl$	239	65·40	7·97	11·73	—	14·88	65·40	8·20	11·32	—	—
20	$C_{14}H_{20}N_2O_2$	248	67·72	8·12	11·28	12·89	—	67·90	8·16	11·15	12·92	—
21	$C_{15}H_{24}N_2$	232	77·53	10·41	12·06	—	—	77·32	10·50	12·19	—	—
22	$C_{16}H_{24}N_2$	244	78·63	9·90	11·46	—	—	78·42	10·05	11·34	—	—

*The compounds were too volatile for a good elementary analysis.

amine to the crude suspension and working up as hereabove (*cf* Tables 1 and 2).

N-Isopropyl-acetonitrilium tetrachloroferrate (3, R = Me; $R^1 = CHMe_2$). To a suspension containing $FeCl_3$ (21 g; 0·13 M) in i-PrCl (78 g) at 0° was added dropwise MeCN (5·4 g; 0·13 m) in a little i-PrCl while stirring. The mixture turned red then yellow and after 3 hr at 0°, the ppt was filtered off; yield: 28 g (81%) of pure 3, R = Me; $R^1 = CHMe_2$; IR (KBr) 5·18 μ.

N-*Isopropyl*-N',N'-*pentamethylene-acetamidine* (5 No. 1) *from* N-*isopropyl-acetonitrilium tetrachloroferrate* 3, R = Me; $R^1 = CHMe_2$. The ice-bath cooled salt 3, (R = Me; $R^1 = CHMe_2$; 31 g) was suspended in 50 ml ether or CH_2Cl_2 and piperidine (10 g) was added dropwise and the mixture worked up as above, yield: 15·8 g, 88% of 5 No. 1.

N-*t-butyl-acetonitrilium tetrachloroferrate* 3, R = Me; $R^1 = CMe_3$. To a suspension of $FeCl_3$ (27 g; 0·167 M) in 40 ml CH_2Cl_2 MeCN (7 g) in 40 ml CH_2Cl_2 was added (color became red due to the complex $(MeCN)_2FeCl_3$). To the ice cooled mixture t-BuCl (15 g; 0·167 M) was added. The color changed from red to yellow. After about 2 hr the solid was filtered off: 33 g, 72% yield of 3, R = Me; $R^1 = CMe_3$.

N-*t-butyl*-N',N'-*pentamethylene acetamidine* (5 No. 14). To the salt 3 (R = Me; $R^1 = CMe_3$; 10 g) suspended in 30 ml CH_2Cl_2 and cooled at 0° a soln containing piperidine (3 g) in 20 ml CH_2Cl_2 was added with stirring. After 1 hr at room temp the solvent was distilled off and the mixture neutralized with 7 g NaOH in 30 ml water and the mixture extracted with ether. The dried organic soln was concentrated and the residue distilled at 110–115° under 12 mmHg gave 2·8 g of 5 No. 14, 46% yield.

N-*Propyl*-N',N'-*pentamethylene acetamidine* 6. To a suspension containing $FeCl_3$ (40 g; 0·25 M), and n-PrCl (78 g; 1 M) MeCN (10 g; 0·25 M) was added dropwise with stirring. The mixture was heated 15 min on a steam bath (HCl began to evolve due to partial decomposition of n-PrCl). The mixture was kept at room temp for 15 hr and to the ice-bath cooled mixture piperidine (21 g) was added dropwise. After work up, the crude amidine was distilled from a 3-bulb tube at 90–140° under high vacuum giving 26 g of a mixture containing 20% of 6 and 80% of 7 (corresponding 5 No. 1) as estimated by NMR.

N-*Isobutyl*-N',N'-*pentamethylene acetamidine* 8. To a suspension of $FeCl_3$ (37 g; 0·22 M) in 100 ml n-BuCl, MeCN (8·2 g; 0·2 M) was added with stirring. The mixture was kept 1 hr at room temp, then heated on a steambath for 1·5 hr (HCl evolved). The excess BuCl was evaporated and CH_2Cl_2 added to the residue. Then piperidine (19 g) were added to the stirred mixture under ice-bath cooling. After 0·5 hr, CH_2Cl_2 was evaporated and 30% NaOH aq (1·1 mole) added to the residue and the mixture extracted with ether. The organic layer was dried with K_2CO_3 and the residue from a concentrated soln distilled at 110°/12 mmHg. The product was contaminated with a little amide which was separated with lactic acid. The amidine 8 was distilled at 210–220°/760 mmHg, yielding 10 g, 25% (Found C, 71·01; H, 12·09; N, 15·04; MW 185; calc. for $C_{11}H_{22}N_2$ C, 72·47; H, 12·16; N, 15·37%; MW 182). The NMR is in agreement with the proposed structure 8.

The same yield of 8 was obtained when the alkylation of MeCN with n-BuCl was carried out during 13 days at room temp.

Bis-N-*isopropyl adiponitrilium tetrachloroferrate* 9. To a suspension of $FeCl_3$ (35 g) in 300 ml i-PrCl, adiponitrile (11 g) was added dropwise. The i-PrCl was heated under reflux and after 6 days at toom temp the solid was filtered off giving 57 g of crude 9. It was identified by hydrolysis: 6 g of 9 in 50 ml water kept 2 days at room temp. The product (1 g; 50% yield) of bis-N-isopropyl-adipamide 10, m.p. 194° was in agreement with the structure 10 (NMR).[10]

N-*t-butylacetamide* 11. To 40 ml of an ethereal soln of $FeCl_3$ (16 g; 0·1 M) cooled in an ice-bath acetonitrile (4g;

0·1 M) was added. The soln became red. Then t-BuOH (7 g) was added and the mixture kept 3 days at room temp. The organic phase was washed with water, dried with Na_2SO_4 and evaporated leaving **11** (1·7 g; 15% yield), m.p. and mixed m.p. 82°.

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