Synthesis of Tetrasubstituted Formamidinium Salts Containing Different *N*-Alkyl Substituents

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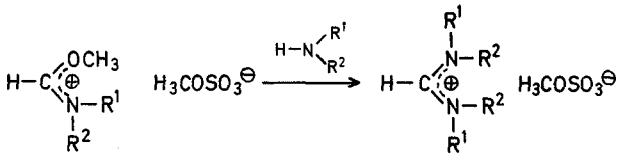
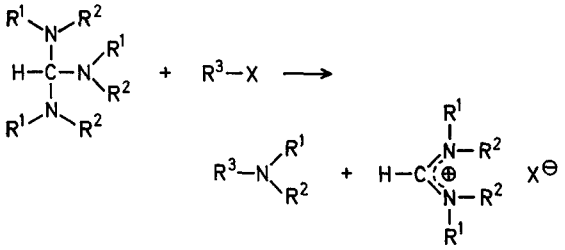
N-Dialkylaminomethylene-*N*-alkylalkanaminium salts, henceforth indicated by their trivial name as formamidinium salts, are versatile starting compounds for a wide range of reactions, including the synthesis of tris[amino]methanes (orthoamides)[1], aminalesters[2], and enamines[3].

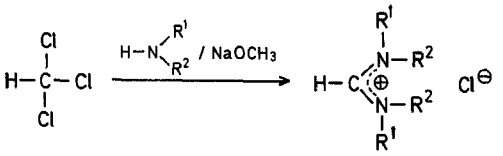
Secondary amines provide the amino groups in the most commonly used synthetic routes to formamidinium salts. As one example of this approach Bredereck et al.[4] treated a dialkylformamide/dimethyl sulphate adduct with a secondary amine to give the salt.



Clemens et al.[5] started with easily accessible orthoamides and treated those with a mineral acid or an alkyl halide to give the salt.

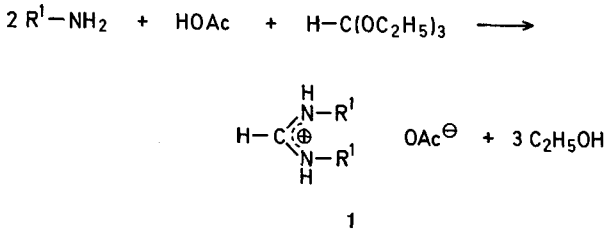


In a third synthesis of formamidinium salts, reported by Scheeren and Nivard[6], secondary amines were treated with chloroform in the presence of sodium methoxide.



Finally, Kantlehner and Speh[7] obtained tetramethylformamidinium chloride in good yield by reaction of thionyl chloride with a three-fold excess of dimethylformamide. So far, this reaction has not been extended to other formamides. In general, only symmetrical secondary amines are readily available. Hence almost all known formamidinium salts are symmetrically substituted at nitrogen.

We have found a simple synthesis of unsymmetrically substituted formamidinium salts which involves a stepwise alkylation procedure.



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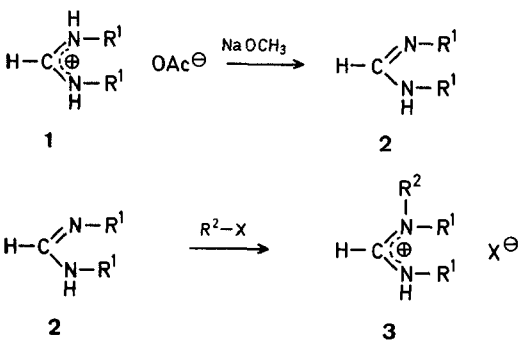

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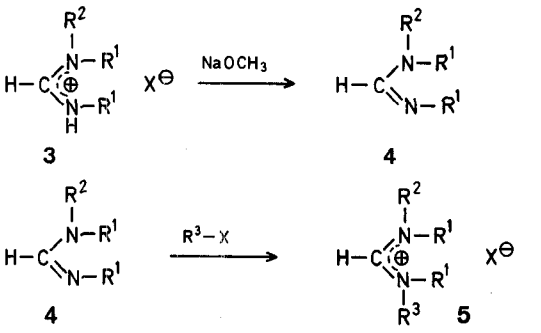
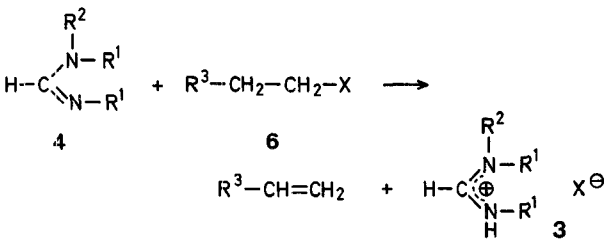


Starting with an *N,N'*-dialkylformamidinium acetate (**1**), prepared according to Taylor and Ehrhart[8], a disubstituted formamidine (**2**) could be obtained by treatment with sodium methoxide. Alkylation of **2** yielded almost quantitatively a trisubstituted formamidinium salt (**3**), which could be converted into a tetrasubstituted salt (**5**) by the same sequence of reactions. The last alkylation step (**4**→**5**) was carried out usually with methyl or ethyl iodide, although benzyl, allyl, and propyl halides also gave satisfactory results. Less reactive alkylating agents such as butyl bromide gave poorer yields, because of contamination of the desired tetrasubstituted salt with a trisubstituted product. This can be ascribed to dehydrohalogenation of the alkyl halide (**6**) under the influence of the strongly basic formamidine (**4**) giving rise to the corresponding alkene and the trisubstituted formamidinium salt (**3**).



To avoid laborious purification of the final formamidinium salts and to obtain these salts in better yields, it appeared advantageous to purify the intermediate trisubstituted formamidines by distillation.

The unsymmetrically substituted formamidinium salts are useful starting compounds in the preparation of other types of compounds which contain secondary amino functions with different alkyl substituents. Thus, unsymmetrical enamines can be obtained without use of a large amount of a less current secondary amine. By hydrolysis, pure unsymmetrical secondary amines themselves can be obtained from these formamidinium salts. Preliminary experiments revealed that the rate of hydrolysis is strongly dependent on the alkylation pattern in the formamidinium salt: the hydrolysis of the *N,N'*-dimethyl-*N,N'*-di-*t*-butylformamidinium iodide is very much slower than that of the *N,N'*-dimethyl-*N,N'*-di-*n*-propyl compound.

Table 1. Preparation of *N,N,N'*-Trialkylformamidines **4**

R^1	R^1	Yield [%][b]	b.p./torr	^{1}H-N.M.R. ($CDCl_3$) δ [ppm] for H—C=
n-C_3H_7	CH_3	37	51°/2	7.2
t-C_4H_9	CH_3	29	68°/20	7.8
CH_3	CH_3	43	106°/760[a]	7.1
$C_6H_5CH_2$	CH_3	31	177°/2	7.5

[a] Lit.[4], b.p. 108°/740 torr.
[b] Based upon starting orthoformate.

Preparation of *N,N'*-Dialkylformamidines (2; *N,N'*-Dialkylmethanimidamides):

N,N'-dialkylformamidinium acetate (**1**), prepared according to Lit.[8] is added to 20% excess of sodium methoxide in methanol. (Dibenzylformamidine is liberated with the aid of sodium carbonate, as described by Taylor.) After stirring at room temperature for 30 min, the reaction mixture is filtered and the methanol evaporated at reduced pressure. The residue is extracted with dry ether. Evaporation of the solvent gives the formamidine; yield: 60–70%.

Preparation of *N,N,N'*-Trialkylformamidinium Halides (3; X = Hal; *N*-(Alkylaminomethylene)-*N*-alkylalkanaminium Halides):

The crude disubstituted formamidine is boiled under reflux for 1 h in dry acetonitrile with 20% excess of an alkyl halide. In

Table 2. Preparation of *N,N,N',N'*-Tetraalkylformamidinium Halides[a] **5**

R^1	R^2	R^3	X	Yield [%]	m.p.[b]	^{1}H-N.M.R. ($CDCl_3$) δ [ppm] for H—C$^{\oplus}$	Mass spectra *m/e*
n-C_3H_7	CH_3	CH_3	J	37	43–45°	8.73	157 ($M^{\oplus}$ – J), 142 ($M^{\oplus}$ – J – CH_3), 127 ($M^{\oplus}$ – J – $2CH_3$)
i-C_3H_7	CH_3	CH_3	J	31	138–140°	8.77	157, 142, 127
t-C_4H_9	CH_3	CH_3	J	28	191–193°	7.97	185, 170, 155
c-C_6H_{11}	CH_3	CH_3	J	29	199–200°	8.52	237, 222, 207
CH_3	CH_3	CH_3	J	43	226–228°	9.20	101, 86, 71
$C_6H_5CH_2$	CH_3	CH_3	J	30	146–148°	9.48	253, 238, 223
$C_6H_5CH_2$	C_2H_5	C_2H_5	J	23	145–147°	9.43	281, 266, 252 ($M^{\oplus}$ – C_2H_5J), 190 ($M^{\oplus}$ – C_7H_7J)
C_6H_5	CH_3	CH_3	J	30	163–165°[c]	8.65–9.49	225, 210, 195
4-H_3CO—C_6H_4	CH_3	CH_3	J	26	113–114°	8.44–9.26	285, 270, 225
4-H_3C—C_6H_4	CH_3	CH_3	J	22	115–116°	8.88–9.22[d]	253, 238, 223
n-C_3H_7	CH_3	$C_6H_5CH_2$	Cl	33	oil	8.72	233, 218, 156 ($M^{\oplus}$ – C_6H_5J)
n-C_3H_7	CH_3	*n*-C_4H_9	Br	15	oil	8.41	199, 184, 156 ($M^{\oplus}$ – C_3H_7J)
n-C_3H_7	*n*-C_3H_7	CH_3	J	27	oil	8.80	185, 170, 142 ($M^{\oplus}$ – C_3H_7J)

[a] No satisfactory analyses could be obtained, due to the extremely hygroscopic character of these salts. Mass spectra however confirmed the assigned structures and no impurities could be detected in the ^{1}H-N.M.R. spectra.
[b] Not corrected.
[c] Lit.[5], m.p. 162–164°; Lit.[9], m.p. 160–161°.
[d] DMSO solution.

most cases, evaporation of the solvent under reduced pressure and washing of the residue with dry ether gives the formamidinium salt nearly quantitatively.

Preparation of *N,N,N'*-Trialkylformamidines (4; *N,N,N'*-Trialkylmethanimidamides):
The formamidines **4** are liberated from their salts **3** by the same procedure as used for products **2**. After purification by distillation, the yields of formamidine are about 60% (Table 1).

Preparation of *N,N,N',N'*-Tetraalkylformamidinium Halides (5; *N*-(Dialkylaminomethylene)-*N*-alkylalkanaminium Halides):
This last step is essentially the same as for salts **3**. Sometimes the very hygroscopic crystals could be purified by recrystallisation from benzene or benzene/cyclohexane (3:1). The yields of tetrasubstituted salts are 80–90%. With butyl bromide as the alkylating agent, the yields do not surpass 40% (Table 2).

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