Rate-Determining Effects in the Formation of *N*-(1-Haloalkyl)heteroarylium Halides

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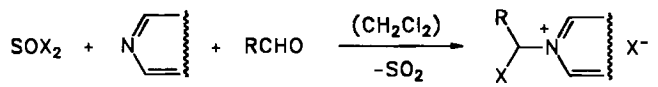
N-(1-Haloalkyl)heteroarylium halides **4** are formed by the reaction of thionyl halides **1** with N-heteroaromatic systems **2** and aldehydes **3**. Kinetic data show the influence of the three types of reagents. A mechanism is proposed for the formation of salts **4**.

Reactions between thionyl halides and N-heteroaromatic systems[1-9], thionyl halides and aldehydes[10], and even between the three species[5,10-12] are well documented. However, in the latter case the heterocycle only acts as a catalyst.

Recently, we have reported[13-16] on the preparation of *N*-(1-haloalkyl)heteroarylium halides **4** from equimolar amounts of a thionyl halide **1**, an N-heteroaromatic system **2**, and an aldehyde **3** (Scheme 1). As the mechanism of this new reaction has not been elucidated, we have monitored the rates of formation of salts **4** by ^{1}H-NMR spectroscopy.

Scheme 1



1 2 3 4

1a: X=Cl
1b: X=Br

2: 1-Methylimidazole, Pyridine, Pyridine Derivatives, Quinoline, Isoquinoline, Pyrimidine, Pyrazine

3: R=Aryl, Alkyl

Rates of Formation of *N*-(1-Chloroalkyl)heteroarylium Chlorides 4 (X = Cl)

Reactions of thionyl chloride (**1a**) with N-heteroaromatic systems **2** and benzaldehyde (**3a**) or 2-methylpropanal (**3b**) have been carried out in dichloromethane. Thus, we have observed that 1-methylimidazole (pK_a = 7.0)[17,18], 3-methylpyridine (pK_a = 5.7), isoquinoline (pK_a = 5.4), pyridine (pK_a = 5.3), and quinoline (pK_a = 4.9) react within 60 min or less to give the corresponding salts **4** in yields exceeding 90%. 3-Bromopyridine (pK_a = 2.8) and pyridine-3-carbonitrile (pK_a = 1.4) are less reactive. The formation of the corresponding salts **4** is slow (see Figures 1 and 2) and sometimes not complete within 24 hours. Therefore, for unhindered aromatic N-heterocycles the rates of formation of *N*-(1-chloroalkyl)heteroarylium chlorides **4** follow qualitatively the basicity of the starting heterocycles **2**.

The dependence on the basicity of the heterocycle is also exhibited in the diazine series (see Figures 1 and 2) and confirmed by the following experiments:

i) Addition of a mixture of benzaldehyde and pyrimidine (pK_a = 1.2) to a mixture of pyridine (pK_a = 5.3) and thionyl chloride (**1a**) in dichloromethane yields the pyridinium salt.

ii) Similarly, addition of a mixture of benzaldehyde and pyridine to a mixture of pyrimidine and **1a** in dichloromethane also yields the pyridinium salt.

2-Phenylpyridine (pK_a = 4.5), despite the fact that its pK_a is in the range of that of pyridine, does not react under similar experimental conditions. 2-Methoxypyridine (pK_a = 3.3) and 2-bromopyridine (pK_a = 0.9) are also not changed in the presence of thionyl chloride and benzaldehyde or 2-methylpropanal. This can be attributed to steric effects in conjunction with the low basicity, especially in the case of 2-bromopyridine.

When a comparison is possible, 2-methylpropanal appears to be more reactive than benzaldehyde. This is illustrated in Figures 1 and 2 for the reactions involving 3-

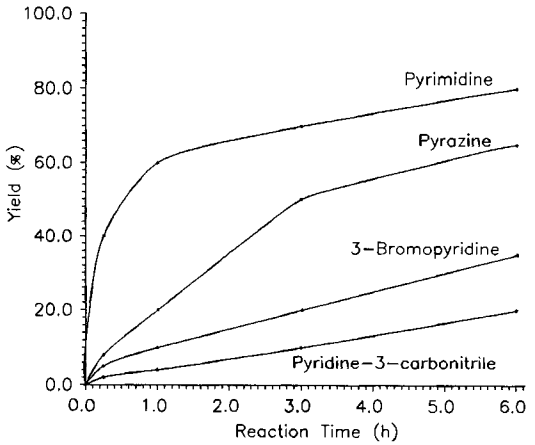


Figure 1. Yield vs time for the formation of some *N*-(α-chlorobenzyl)heteroarylium chlorides **4** (R = C_6H_5, X = Cl) as a function of the starting heterocycle **2**

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bromopyridine, pyridine-3-carbonitrile, pyrimidine, or pyrazine. Therefore, the rate of formation of 1-(chloroalkyl)-heteroarylium chlorides **4** is also dependent on the nature of the starting aldehydes **3**. Further examples of steric and electronic effects are given in Table 1.

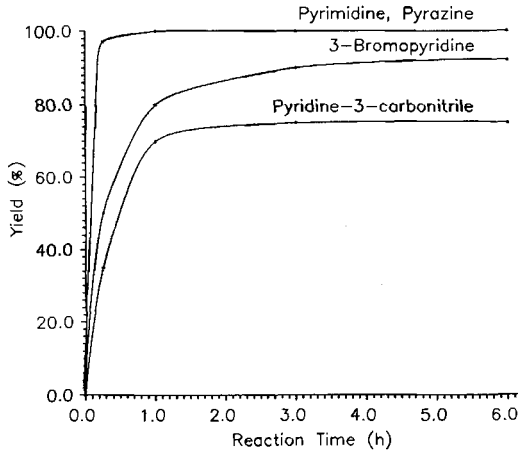


Figure 2. Yield vs time for the formation of some *N*-(1-chloro-2-methylpropyl)heteroarylium chlorides **4** (R = *i*Pr, X = Cl) as a function of the starting heterocycle **2**

Concentration Effects

Thionyl bromide (**1b**) is more reactive than thionyl chloride (Table 2) but more difficult to handle. Therefore, we have preferred the use of thionyl chloride for the study of concentration effects. For a given reaction time, the yields of 3-bromo-*N*-(α-chlorobenzyl)pyridinium chloride (**4m**, Table 4) are proportional to the concentration of the starting heterocycle (Table 2). Furthermore, the results of our investigation clearly indicate that the rate of formation of **4m** is also enhanced when an excess of thionyl chloride or benzaldehyde is used.

Suggested Reaction Pathway

As the rate of formation of *N*-(1-haloalkyl)heteroarylium halides **4** depends on the concentration and on the nature of each of the three components, we may reasonably propose that the reactions proceed via a preequilibrium between two of the three reactants. The three possibilities are considered hereafter.

Preequilibrium Between the Thionyl Halide and the Aldehyde

We can exclude that *N*-(1-haloalkyl)heteroarylium halides arise from a reaction between the heterocycle **2** and any adduct formed from the thionyl halide **1** and the aldehyde **3**. Indeed, benzaldehyde (**3a**) is rather stable[19] in the presence of thionyl chloride. On the other hand, 2-methylpropanal (**3b**) reacts with one equivalent of thionyl chloride (without pyridine) to yield a complex mixture of products. Its ^{1}H-NMR spectrum reveals the presence of a major component characterized by a singlet (δ = 1.8) assigned to six protons of two magnetically equivalent methyl groups and a second singlet (δ = 9.8) assigned to an aldehyde proton. Attempts to identify this aldehyde by GC/MS analysis have been unsuccessful due to degradation. 2-(Chlorosulfinyl)-2-methylpropanal (**5**) (Scheme 2) is assumed to be formed.

Similar adducts are known to be generated when thionyl chloride is treated with isopropyl ketones[20] or 2-

Table 1. Rates of formation of some *N*-(1-chloroalkyl)heteroarylium chlorides **4** from thionyl chloride (**1a**), an N-heterocycle **2** and an aldehyde **3**

Heterocycle **2**	RCHO **3** R	Yield[a] of **4** (%) Reaction time [h] 0.25	1	3	6	24
Pyridine	**a** C_6H_5	[b]				
Pyridine	**b** *i*Pr	[b]				
Pyridine	**c** *t*Bu	60	80	80	80	80
3-Bromopyridine	**a** C_6H_5	<10[c]	<10[c]	20	35	65
3-Bromopyridine	**d** 4-(NC)C_6H_4	<10[c]	<10[c]	<10[c]	20	60
3-Bromopyridine	**e** 4-(CH_3O)C_6H_4	<10[c]	15	45	65	80
3-Bromopyridine	**b** *i*Pr	50	80	90	90	90
3-Bromopyridine	**c** *t*Bu	<10[c]	<10[c]	10	15	45
Pyrimidine	**a** C_6H_5	40	60	70	80	90
Pyrimidine	**b** *i*Pr	[b]				
Pyrimidine	**c** *t*Bu	25	40	70	70	70

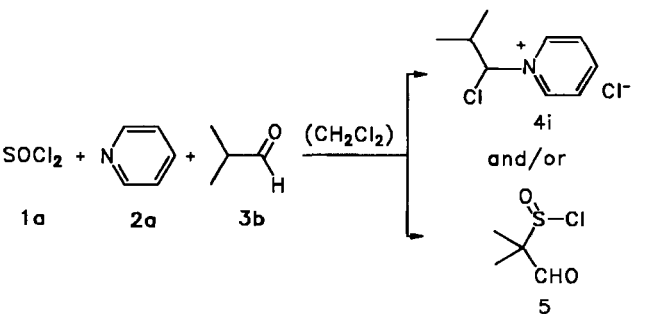
[a] Calculated relative to the aldehyde concentration. — [b] Complete disappearance of the aldehyde. — [c] The corresponding salt is detected but the yield is only estimated.

Table 2. Concentration effects on the rates of formation of 3-bromo-*N*-(α-halobenzyl)pyridinium halides **4** from a thionyl halide **1**, 3-bromopyridine, and benzaldehyde

SOX_2 X	Stoichiometric coefficient SOX_2	3-BrC_5H_4N	C_6H_5CHO (**3a**)	Yield[a] of **4** (%) Reaction time [h] 1	3	6
Br	1.2	1.2	1	50	70	80
Cl	1.2	1.2	1	<10[c]	20	35
Cl	1.2	2	1	20	40	70
Cl	1.2	3	1	50	70	85
Cl	1.2	4	1	60	70	90
Cl	1.2	5	1	70	90	95
Cl	1.2	1.2	5[b]	50	60	60
Cl	5	1.2	1	75	85	90

[a] Calculated relative to the aldehyde concentration. — [b] Yields are probably slightly underestimated as thionyl chloride may be involved in the formation of benzyl dichloride[19] or in a reaction with benzoic acid (oxidation product of benzaldehyde). — [c] The corresponding salt is detected by ^{1}H-NMR spectroscopy but the yield is only estimated.

Scheme 2



methylpropionitrile[21]. The formation of the α-chlorosulfinyl aldehyde **5** is favored by the presence of small quantities of pyridine (**2a**) in the medium (Table 3). However, for significant concentrations of pyridine, the formation of *N*-(1-chloro-2-methylpropyl)pyridinium chloride (**4i**) (Scheme 2) is the kinetically preferential process. Let us mention that the α-chlorosulfinyl aldehyde **5** is not a precursor of a pyridinium salt of type **4**. When formed, it reacts neither with pyridine nor with a mixture of thionyl chloride and pyridine.

Table 3. Influence of the concentration of pyridine on the reaction with thionyl chloride (**1a**) and 2-methylpropanal (**3b**), competitive formation of **4i** and **5**

Pyridine (**2a**) Stoichiometric coefficient	Formation of **5** (%) Reaction time [h] 0.25	1	3	6
0	10	20	30	35
(Catalytic amount)	10	40	40	40
0.10	55	65	70	75
0.20	50	65	70	70

Composition of the reaction mixture after 1 h:

Pyridine (**2a**) Stoichiometric coefficient	Formation of **5** (%)	**4i** (%)
0.10	65	not detected
0.20	65	not detected
0.30	60	25
0.40	55	30
0.50	50	35
0.75	20	65
1.00	<10	>90

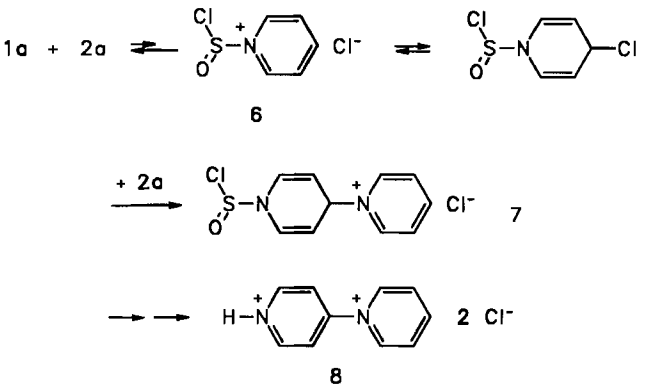
Preequilibrium Between the Thionyl Halide and the Heterocycle

Thionyl halides **1** and N-heteroaromatic systems **2** are known[1-9] to be in equilibrium with the corresponding 1-(halosulfinyl)heteroarylium halides. However, 1-(chlorosulfinyl)pyridinium chloride, (**6**), for example, readily adds a second molecule of **2a** to yield[2-4,8] *N*-[1-(chlorosulfinyl)-1,4-dihydropyridin-4-yl]pyridinium chloride (**7**), the intermediate probably involved in the preparation[2,4] of *N*-(pyridin-4-)pyridinium chloride hydrochloride (**8**, Scheme 3). None of those salts has been detected in our experiments. Furthermore, we have observed that the stable thionyl chloride/4-(dimethylamino)pyridine complex[7] does not react with aldehydes in dichloromethane, chlorobenzene, or even dimethyl sulfoxide. Therefore, it seems unlikely that such complexes yield *N*-(1-haloalkyl)heteroarylium halides **4**.

Preequilibrium Between the Heterocycle and the Aldehyde

Although adducts **9** (Scheme 4) between aromatic N-heterocycles and aldehydes have never been detected spectroscopically, their existence has been proposed earlier[13,22]. Furthermore, detectable betainic structures with comparable constituents result from the interaction between nitrogen bases and some carbonyl compounds whose electrophilicity is enhanced[27]. For example, the existence of the adduct of *p*,α,α,α-tetrafluoroacetophenone and 1,4-diazabicyclo[2.2.2]-octane (DABCO) in acetone has been proven by ^{13}C-NMR spectroscopy. The addition of a fivefold excess of DABCO to this and related trifluoroacetophenones results in the complete disappearance of the carbonyl stretching band at 1791 cm^{-1} [27].

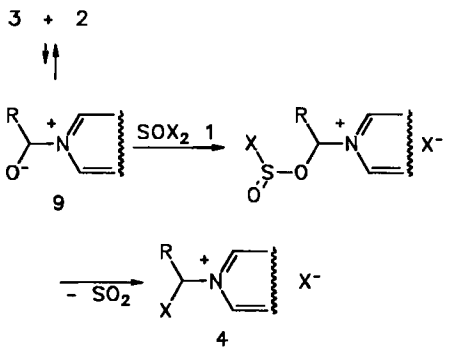
Scheme 3



X-ray investigations indicate a weak interaction between the lone pair of the amino N and the carbonyl C atoms of 1-(dimethylamino)-8-acetylnaphthalene[28]. Therefore, we assume that "zwitterions" **9** are the reactive species involved in the formation of *N*-(1-haloalkyl)heteroarylium halides **4**. Indeed, they can readily react with thionyl halides by *O*-sulfinylation[5,10]. Followed by a quasi-intramolecular substitution and the elimination of sulfur dioxide, the salts **4** are formed (Scheme 4).

These arguments are in good agreement with our kinetic data as the formation of the heterocycle/aldehyde complexes must depend on the nature of the heterocycle **2** (pK_a, steric hindrance, number of nitrogen atoms) and on the nature[23-26] of the aldehyde (aromatic or aliphatic, steric hindrance).

Scheme 4



Conclusions

Studies on the rates of formation of *N*-(1-haloalkyl)heteroarylium halides **4** have stimulated us to use a wide range of reactants. From the results, the generality of the reaction

of a thionyl halide **1** with an aromatic N-heterocycle **2** and an aldehyde **3** is evident.

From a practical point of view, we wish to emphasize that the experimental procedure is easy and that the conditions applied are very mild. Side reactions are rare or slow. The method is however limited by the poor reactivity of some heterocycles bearing a substituent in the α-position of the nitrogen atom.

Studies on the behavior of *N*-(1-haloalkyl)heteroarylium halides **4** towards nucleophiles are in progress in our laboratories.

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Experimental

Materials: Reagents are commercially available and were purified, if necessary, by classical methods (distillation or recrystallization). Dichloromethane was distilled and dried over molecular sieves.

General Procedure[13–16] *for the Preparation of N-(1-Haloalkyl)-heteroarylium Halides* **4a–x** (Table 4): A 1 M solution of the thionyl halide **1** in dichloromethane (12 ml) was cooled to 0°C under nitrogen. A 2 M solution of the heterocycle **2** in dichloromethane (6 ml) was added dropwise followed by a 2 M solution of the aldehyde **3** in dichloromethane (5 ml). The solution was allowed to warm to room temp. The salts **4** were not isolated but characterized by their ^{1}H-NMR data. Relevant signals are given in Table 4.

Kinetic Data: Reactions were monitored by ^{1}H-NMR (Varian EM 360-L) spectrometry using dichloromethane as a solvent; most of the salts **4** were soluble. Quantitative data were obtained by a comparison of the integrated intensities of peaks due to the alde-

Table 4. Relevant peaks in the ^{1}H-NMR spectra of *N*-(1-haloalkyl)heteroarylium halides **4a–x**

Starting heterocycle **2**	Salt **4**	X	R	δ values[a] Heterocyclic moiety	*CHX*
1-Methylimidazole	**4a**	Cl	C_6H_5	10.2(s)	8.3(s)
1-Methylimidazole	**4b**	Cl	iPr	[b]	
3-Methylpyridine	**4c**	Cl	C_6H_5	9.7(s), 9.6(d)	9.1(s)
3-Methylpyridine	**4d**	Cl	iPr	9.7(s), 9.6(d), 8.6(t), 8.2(d)	7.3(d)
Isoquinoline	**4e**	Cl	C_6H_5	11.4(s), 8.9(d)	9.1(s)
Isoquinoline	**4f**	Cl	iPr	11.2(s), 8.9(d), 8.6(t)	7.2(s)
Pyridine	**4g**	Cl	C_6H_5	9.8(d), 8.8(d), 8.3(t)	9.2(s)
Pyridine	**4h**	Br	C_6H_5	9.7(d), 8.8(t), 8.3(t)	9.0(s)
Pyridine	**4i**	Cl	iPr	9.7(d), 8.7(t), 8.2(t)	7.2(d)
Pyridine	**4j**	Cl	tBu	[b]	
Quinoline	**4k**	Cl	C_6H_5	10.0(d), 9.4(d)	9.5(s)
Quinoline	**4l**	Cl	iPr	10.2(d), 9.4(d)	7.4(d)
3-Bromopyridine	**4m**	Cl	C_6H_5	9.8(s), 9.7(d)	9.0(s)
3-Bromopyridine	**4n**	Cl	iPr	10.1(s), 9.8(d), 8.7(t), 8.3(t)	7.5(d)
3-Bromopyridine	**4o**	Cl	$4(NC)C_6H_4$	10.1(s), 9.8(d)	9.3(s)
3-Bromopyridine	**4p**	Cl	$4(CH_3O)C_6H_4$	9.8(s), 9.7(d)	8.9(s)
3-Bromopyridine	**4q**	Cl	tBu	10.0(s), 9.7(d)	7.9(s)
Pyridine-3-carbonitrile	**4r**	Cl	C_6H_5	10.3(s), 10.1(d)	9.1(s)
Pyridine-3-carbonitrile	**4s**	Cl	iPr	[b]	
Pyrimidine	**4t**	Cl	C_6H_5	10.4(s), 10.0(d), 9.5(d), 8.5(t)	9.0(s)
Pyrimidine	**4u**	Cl	iPr	10.6(s), 10.2(d), 9.7(d), 8.6(t)	7.5(d)
Pyrimidine	**4v**	Cl	tBu	10.5(s), 10.0(d), 9.7(d), 8.6(t)	7.6(s)
Pyrazine	**4w**	Cl	C_6H_5	9.7(2d)	9.0(s)
Pyrazine	**4x**	Cl	iPr	9.8(2d)	7.6(d)

[a] Solvent: CH_2Cl_2; δ = 5.4. – [b] Badly resolved.

hydic proton and the heteroaryl(ium) moiety; side reactions occured rarely[16] or slowly (vide supra). An alternative procedure resulted from a comparison of the integrated intensity of the aldehyde peak in the spectrum of solutions of known concentration.

pK_a values are those reported in ref.[17,18].

CAS Registry Numbers

1a: 7719-09-7 / **1b**: 507-16-4 / **2a**: 110-86-1 / **3a**: 100-52-7 / **3b**: 78-84-2 / **3c**: 630-19-3 / **3d**: 105-07-7 / **3e**: 123-11-5 / **4a**: 133753-70-5 / **4b**: 133753-71-6 / **4c**: 133753-72-7 / **4d**: 133753-73-8 / **4e**: 133753-74-9 / **4f**: 133753-75-0 / **4g**: 127896-76-8 / **4h**: 122699-86-9 / **4i**: 133753-76-1 / **4f**: 133753-77-2 / **4k**: 133753-78-3 / **4l**: 133753-79-4 / **4m**: 133753-80-7 / **4n**: 133753-81-8 / **4o**: 133753-82-9 / **4p**: 133753-83-0 / **4q**: 133753-84-1 / **4r**: 133753-85-2 / **4s**: 133753-86-3/ **4t**: 127896-78-0 / **4u**: 133753-87-4 / **4v**: 133753-88-5 / **4w**: 133753-89-6 / **4x**: 133753-90-9 / **5**: 89089-39-4 / 1-methylimidazole: 616-47-7 / 3-methylpyridine: 108-99-6 / isoquinoline: 119-65-3 / quinoline: 91-22-5 / 3-bromopyridine: 626-55-1 / pyridine-3-carbonitrile: 100-54-9 / pyrimidine: 289-95-2 / pyrazine: 290-37-9

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