Notiz / Note

Rate-Determining Effects in the Formation of Hantzsch 1,4-Dihydropyridines from *N*-(1-Haloalkyl)azinium Halides and Methyl 3-Amino-2-butenoate

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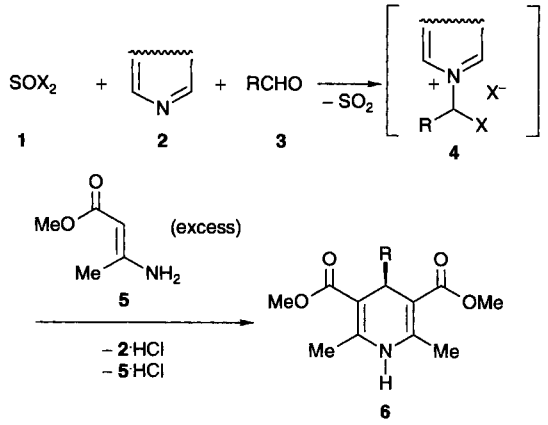
N-(1-Haloalkyl)azinium halides react with methyl 3-amino-2-butenoate to yield 4-substituted dimethyl 1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylates. The rates of formation of the latter compounds are monitored by ^{1}H-NMR spectroscopy. Mechanistic and practical considerations are discussed.

Recently, we have reported[1,2] on the formation of *N*-(1-haloalkyl)azinium halides **4** from equimolar amounts of a thionyl halide **1**, an N-heteroaromatic system **2**, and an aldehyde **3** (Scheme 1). Such salts are efficient precursors for the synthesis of a wide range of heterocycles among which are imidazolidines[3] and 1,4-dihydropyridines[4]. As we needed to improve experimental procedures[5], it was imperative to collect kinetic data in order to determine the various factors governing the reactivity of salts **4**. In addition this would be an important source of mechanistic information. We decided to monitor the formation of 4-substituted dimethyl 1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylates **6** from (not isolated) *N*-(1-haloalkyl)azinium halides **4** and methyl 3-amino-2-butenoate (**5**) (Scheme 1) under experimental conditions that are particularly suitable for a quantitative ^{1}H-NMR study. Indeed, syntheses can be carried out at room temperature in dichloromethane in which both reactants and final products are soluble. They give rise to typical signals that do not interfere with the solvent peak and that do not overlap. Moreover, side reactions are rare.

It has been suggested earlier[1] that *N*-(1-haloalkyl)azinium halides **4** react with nucleophiles by displacement of the halogen atom in the rate-determining step. Our results confirm this since *N*-[bromo(phenyl)methyl]pyridinium bromide (**4a**) reacts faster than *N*-[chloro(phenyl)methyl]pyridinium chloride (**4b**) (Table 1, first block). Moreover, reactions involving *N*-(1-chloroalkyl)azinium chlorides derived from aromatic aldehydes are faster than those involving salts derived from aliphatic aldehydes (Table 1, second block). We have also observed that *N*-[chloro(phenyl)methyl]pyridinium chloride (**4b**) is less reactive than salts obtained from substituted benzaldehydes whatever the nature of the substituent (electron-withdrawing or electron-donating). This parallels the reactivity of benzyl chlorides towards the thiosulfate ion[6,7]: the rates are represented by a series of U-shaped Hammett equation plots. Since such reactions are believed to proceed via an S_N2 mechanism, the latter should apply to syntheses involving salts **4**.

We also determined the effect of the heteroarenium moiety on the behavior of salts **4**. For this purpose, *N*-[chloro(phenyl)methyl]-azinium chlorides and the analogous *N*-(1-chloro-2-methylpropyl)azinium chlorides were prepared and subjected to reaction with methyl 3-amino-2-butenoate (**5**) (Table 1, third and fourth block). In both series a dramatic influence of the electron-withdrawing strength of the heteroarenium group was observed: pyrimidinium

Scheme 1



SOX_2 **1** X	Heterocycle **2**	RCHO **3** R	Salt **4**	Product **6**
Br (**1a**)	Pyridine (**2a**)	C_6H_5 (**3a**)	(**4a**)	(**6a**)
Cl (**1b**)	Pyridine (**2a**)	C_6H_5 (**3a**)	(**4b**)	(**6a**)
Cl (**1b**)	Pyridine (**2a**)	*i* Pr (**3b**)	(**4c**)	(**6b**)
Cl (**1b**)	Pyridine (**2a**)	4-(NC)C_6H_4 (**3c**)	(**4d**)	(**6c**)
Cl (**1b**)	Pyridine (**2a**)	4-(H_3CO)C_6H_4 (**3d**)	(**4e**)	(**6d**)
Cl (**1b**)	3-Me-Pyridine (**2b**)	C_6H_5 (**3a**)	(**4f**)	(**6a**)
Cl (**1b**)	3-Br-Pyridine (**2c**)	C_6H_5 (**3a**)	(**4g**)	(**6a**)
Cl (**1b**)	Isoquinoline (**2d**)	C_6H_5 (**3a**)	(**4h**)	(**6a**)
Cl (**1b**)	Pyrimidine (**2e**)	C_6H_5 (**3a**)	(**4i**)	(**6a**)
Cl (**1b**)	3-Me-Pyridine (**2b**)	*i* Pr (**3b**)	(**4j**)	(**6b**)
Cl (**1b**)	3-Br-Pyridine (**2c**)	*i* Pr (**3b**)	(**4k**)	(**6b**)
Cl (**1b**)	Isoquinoline (**2d**)	*i* Pr (**3b**)	(**4l**)	(**6b**)
Cl (**1b**)	Pyrimidine (**2e**)	*i* Pr (**3b**)	(**4m**)	(**6b**)

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Table 1. Time dependence of the formation of dihydropyridines **6** (Scheme 1)

			6a [%] from	
Time [h]			**4a**	**4b**
0.25			40	20
1			75	45
3			90	60
			6 [%] from	
	4e	**4d**	**4b**	**4c**
0.25	75	60	25	10
1	95	90	45	20
3			60	30
			6a [%] from	
	4g, 4h, 4i		**4b**	**4f**
0.25	>95		20	<10
1			40	10
3			60	30
24			>95	60
			6b [%] from	
	4l, 4m	**4k**	**4c**	**4j**
0.25	>95	20	10	<10
1		45	15	<10
3		70	30	<10
24		95	95	<10

and isoquinolinium salts are the most reactive, followed by the pyridinium salts bearing (on the heterocycle) an electron-withdrawing group, then by the pyridinium salt (unsubstituted on the heterocycle), and finally, by the pyridinium salts bearing (on the heterocycle) an electron-donating group.

From a practical viewpoint, our data reveal that conversion of aldehydes into the corresponding *N*-(1-haloalkyl)azinium halides is a useful reaction for benzaldehydes bearing an electron-withdrawing group: the latter react poorly (at the carbon atom of the carbonyl function) in comparison with benzaldehyde itself or with aliphatic aldehydes. Conversion into the salts allows to reverse that classical sequence. In addition, when overall yields are good, they depend only slightly on the nature of the heterocycle used to effect the conversion. Therefore, compromises between the rate of formation of *N*-(1-haloalkyl)azinium halides[2] and their reactivity can be found. Finally, the wide range of applicability of the reaction yielding *N*-(1-haloalkyl)azinium halides enables us to choose the most appropriate heterocycle according to other special requirements such as the ease of the workup procedure, the necessity to recycle the heterocycle, its solubility in various solvents, etc.

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Experimental

Melting points (uncorrected): Hot-stage microscope. – IR: Perkin-Elmer 577. – ^{1}H NMR: Varian EM-360 L (TMS as internal standard). – Elemental analyses: *Station de Haute-Belgique* (Libramont-Chevigny; Belgium). – 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[2,4] A solution of thionyl halide (12 mmol) in dichloromethane (12 ml) was cooled to 0°C. A solution of the heterocycle (12 mmol) in dichloromethane (6 ml) was added dropwise, followed by a solution of the aldehyde (10 mmol) in dichloromethane (5 ml). The mixture was allowed to warm to room temperature until complete disappearance of the aldehyde (reaction times have been reported[2]). Methyl 3-amino-2-butenoate[4] [3.45 g (30 mmol)] was added slowly, and samples of the reaction mixture were analyzed regularly by ^{1}H NMR. Side reactions occurred rarely or slowly[4,8], so that quantitative data were obtained by measuring the decrease of the integrated intensities of peaks due to the heteroarenium moiety. Compounds **4a**[1], **b**[8], **c**[2], **d**[9], **e**[3], **f**[2], **g**[2], **h**[2], **i**[8], **j**[8], **k**[2], **l**[2], **m**[2], **6a**[10], **c**[11] have been described in the literature, and they were fully characterized on the basis of their spectral data.

Dimethyl 1,4-Dihydro-4-(1-methylethyl)-2,6-dimethyl-3,5-pyridinedicarboxylate (**6b**): **6b** from **4m** and **5** [2.89 g, (90%)], m.p. 168–169°C [EtOH/H_2O (1:1)]. – IR (KBr): $\tilde{\nu}$ = 3320 cm^{-1} (N–H), 1680 (C=O). – ^{1}H NMR ($CDCl_3$): δ = 0.8 [d, J = 7 Hz, 6H, $CH(CH_3)_2$], 1.5 [m, J = 7 Hz, 1H, $CH(CH_3)_2$], 2.3 (s, 6H, 2-, 6-CH_3), 3.7 (s, 6H, OCH_3), 3.9 (d, J = 7 Hz, 1H, 4-H), 6.1 (br. 1H, NH).

$C_{14}H_{21}NO_4$ (267.3) Calcd. C 62.90 H 7.92 N 5.24
Found C 63.27 H 8.06 N 5.25

Dimethyl 1,4-Dihydro-4-(4-methoxyphenyl)-2,6-dimethyl-3,5-pyridinedicarboxylate (**6d**): **6d** from **4e** and **5** [3.58 g, (90%)], m.p. 192–194°C (EtOH). – IR (KBr): $\tilde{\nu}$ = 3350 cm^{-1} (NH), 1690 (C=O). – ^{1}H NMR ($CDCl_3$): δ = 2.3 (s, 6H, 2-, 6-CH_3), 3.7 (s, 6H, CO_2CH_3), 3.8 (s, 3H, OCH_3), 4.9 (s, 1H, 4-H), 6.1 (br. 1H, NH), 6.6–7.3 (m, 4H, aromatic H).

$C_{18}H_{21}NO_5$ (331.4) Calcd. C 65.24 H 6.39 N 4.23
Found C 65.57 H 6.33 N 4.26

[1] E. Anders, J. G. Tropsch, A. R. Katritzky, D. Rasala, J.-J. Vanden Eynde, *J. Org. Chem.* **1989**, *54*, 4808.
[2] A. Maquestiau, E. Anders, A. Mayence, J.-J. Vanden Eynde, *Chem. Ber.* **1991**, *124*, 2013.
[3] J.-J. Vanden Eynde, A. Mayence, A. Maquestiau, E. Anders, *Bull. Soc. Chim. Belg.* **1992**, *101*, 233.
[4] J.-J. Vanden Eynde, P. D'Orazio, A. Mayence, A. Maquestiau, E. Anders, *Tetrahedron* **1992**, *48*, 1263.
[5] UCB s.a. (Inv.: A. Maquestiau, A. Mayence, J.-J. Vanden Eynde, J.-C. Vanovervelt, A. Van Gysel), GB 9108279.2 (April 18, 1991).
[6] R. Fuchs, D. M. Carleton, *J. Am. Chem. Soc.* **1963**, *85*, 104.
[7] T. H. Lowry, K. Schueller Richardson, *Mechanism and Theory in Organic Chemistry*, Harper and Row Publishers, New York **1976**, p. 182.
[8] A. Maquestiau, E. Anders, J.-J. Vanden Eynde, P. D'Orazio, A. Mayence, *Bull. Soc. Chim. Belg.* **1989**, *98*, 523.
[9] J.-J. Vanden Eynde, J. Godin, A. Mayence, A. Maquestiau, E. Anders, *Synthesis*, in press.
[10] A. P. Phillips, *J. Am. Chem. Soc.* **1949**, *71*, 4003.
[11] Bayer s.a. (Inv.: F. Bossert, W. Vater), Ger. Offen. 1963188 (December 17, 1969); *Chem. Abstr.* **1971**, *75*, P 63618b.

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