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Novel Syntheses of Heterocycles with N-(1-Haloalkyl)azinium Halides. Part 2.[1] Preparation of N-Unsubstituted 1,4-Dihydropyridines

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Abstract: N-(1-Chloroalkyl)pyridinium chlorides, prepared from thionyl chloride, pyridine, and aldehydes, readily react with enaminocarbonyl derivatives to yield 1,4-dihydropyridines under mild and neutral conditions.

In a previous paper[2] we showed that preparation of imines from poorly nucleophilic and/or poorly soluble amines can easily be achieved by a one-pot method involving conversion of aldehydes into the corresponding N-(1-chloroalkyl)azinium salts (see Figure). That result led us to study the chemical behaviour of those salts towards enaminocarbonyl compounds. Indeed the latter are characterized by a strong interaction between the nitrogen lone pair and the pi electrons of the double bonds. As a consequence the amino function is poorly reactive and electrophiles often attack the carbon atom bearing the carbonyl group. Aldehydes, for example, are known to react with 3-amino-2-butenoates to yield 1,4-dihydropyridines[3] but not imines.

Thus a solution of N-(chlorophenylmethyl)pyridinium chloride (**1g**), prepared from thionyl chloride, pyridine, and benzaldehyde in dichloromethane,[2] was reacted with 3 equivalents of ethyl 3-amino-2-butenoate. After several hours the solvent was evaporated and the residue was triturated with water to

afford a crude product identified (nmr, I.R., M.S.) as diethyl 1,4-dihydro-2,6-dimethyl-4-phenyl-3,5-pyridinedicarboxylate (2g).

Therefore, 1g behaves like the corresponding aldehyde. However, we observed that, in dichloromethane at room temperature, salt 1g is more reactive than benzaldehyde towards ethyl 3-amino-2-butenoate. Indeed, under such conditions, benzaldehyde does not react with the enaminoester (yield in 2g : less than 5% after 48 hours) whereas from 1g we could obtain the dihydropyridine 2g with a yield of 88% after a reaction time of 8 hours.

At the end of the reaction we detected, beside the dihydropyridine, free pyridine, ammonium chloride, and the hydrochloride of the enaminocarbonyl compound. Therefore we suggest[4] that one molecule of salt reacts with two molecules[5] of the enaminocarbonyl compound to yield the intermediate **A** (see Figure) which could protonate on one amino function thus creating an excellent leaving group ($-NH_3^{(+)}$) for ring closure (for a better understanding of the Figure, the enaminocarbonyl compounds are represented under the E form[7-10]).

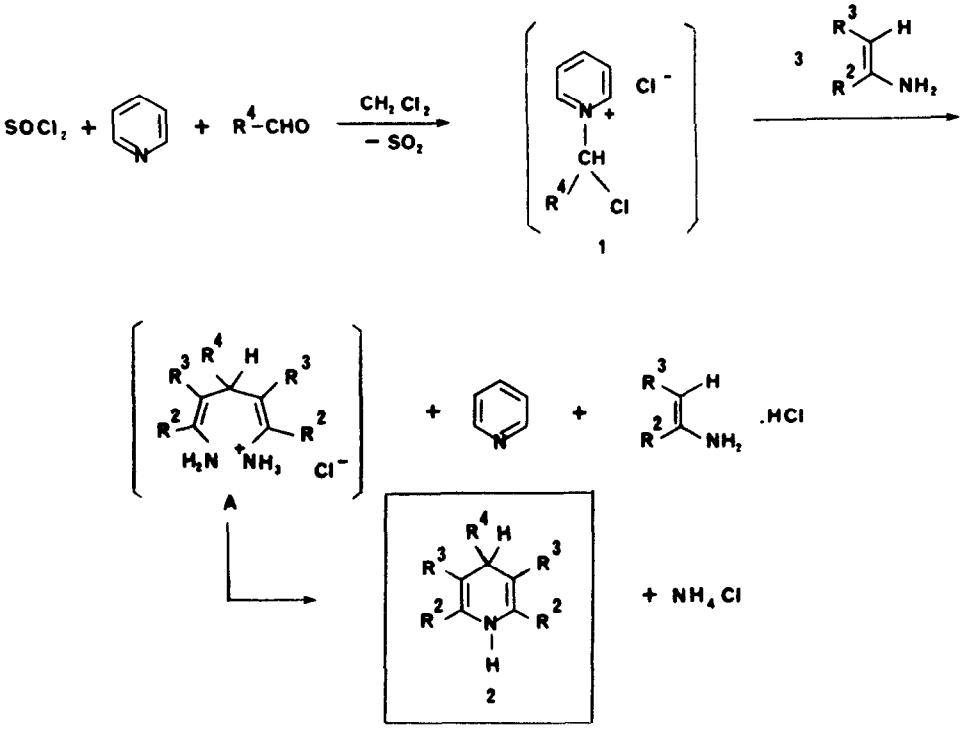

Fig. Suggested pathway for the formation of 1,4-dihydropyridines (2) from N-(chloroalkyl)pyridinium chlorides (1) and enaminocarbonyl derivatives

To test the generality of that novel method for the preparation of 1,4-dihydropyridines, fifteen salts (1a-1o) were used to be subjected to reaction with ethyl 3-amino-2-butenoate. This way, we obtained the dihydropyridines 2a-2g (Table). We could also extend the procedure to reactions involving other enaminocarbonyl derivatives as illustrated in the Table.

Table. 1,4-Dihydropyridines (2) Prepared from N-(1-Chloroalkyl)pyridinium Chlorides (1) and Enaminocarbonyl Derivatives

Salt	Product	R^2	R^3	R^4	Overall yield (%)[a]	Reported yield (%)[b]
1a	2a	CH_3	$CO_2C_2H_5$	C_2H_5	88	c
1b	2b	CH_3	$CO_2C_2H_5$	C_3H_7	78	c
1c	2c	CH_3	$CO_2C_2H_5$	$(CH_3)_2CH$	78	61[6]
1d	2d	CH_3	$CO_2C_2H_5$	C_6H_5-CH_2	80	61[6]
1e	2e	CH_3	$CO_2C_2H_5$	$(C_6H_5)_2CH$	65	25[11]
1f	2f	CH_3	$CO_2C_2H_5$	$(C_6H_5)(CH_3)CH$	75	-
1g	2g	CH_3	$CO_2C_2H_5$	C_6H_5	88	50[6]
1h	2h	CH_3	$CO_2C_2H_5$	4-CH_3-C_6H_4	90	c
1i	2i	CH_3	$CO_2C_2H_5$	4-CH_3O-C_6H_4	90	c
1j	2j	CH_3	$CO_2C_2H_5$	2-NO_2-C_6H_4	95	50[6,d]
1k	2k	CH_3	$CO_2C_2H_5$	3-NO_2-C_6H_4	95	80[12]
1l	2l	CH_3	$CO_2C_2H_5$	4-NO_2-C_6H_4	95	c
1m	2m	CH_3	$CO_2C_2H_5$	4-Cl-C_6H_4	95	c
1n	2n	CH_3	$CO_2C_2H_5$	2-furyl	95	81[6]
1o	2o	CH_3	$CO_2C_2H_5$	2-thienyl	95	77[6]
1l	2p	CH_3	$CO_2C(CH_3)_3$	4-NO_2-C_6H_4	80	c
1l	2q	CH_3	$COCH_3$	4-NO_2-C_6H_4	90	27[13]
1l	2r	CH_2-$C(CH_3)_2$-CH_2-C=O		4-NO_2-C_6H_4	80	67[14]
1l	2s	CH_3	CN	4-NO_2-C_6H_4	80	45[15,e]

[a]: based on the aldehyde; [b]: for a classical Hantzsch reaction except in the case of 2s; [c]: not mentioned; [d]: for the dimethyl ester; [e]: from 4-nitrobenzaldehyde and 3-amino-2-butenitrile.

In all cases the corresponding 1,4-dihydropyridines were obtained in good yields always better than those reported in the literature (for the synthesis of the same derivatives from aldehydes) and under milder conditions (dichloromethane at room temperature versus boiling ethanol). For example, from salt **1e** we isolated the 1,4-dihydropyridine **2e** substituted by a diphenylmethyl group at the 4-position with a not optimized yield of 65%. The same reaction performed with diphenylacetaldehyde affords **2e** with a yield of 25%.[11] Another benefit of our method is emphasized by the preparation of the 4-(2-nitrophenyl)-1,4-dihyropyridine **2j**. It was isolated with an overall yield of 90% whereas ortho-substituted benzaldehydes are known to be poorly reactive towards enaminoesters.[6]

Mention should also be made that our procedure does not require isolation of the intermediate N-(1-chloroalkyl)pyridinium chlorides and that our experiments were carried out at room temperature.

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EXPERIMENTAL

Compounds **1a**,[5] **1b**,[1] **1c**,[16] **1e**,[5] **1g**,[2] **1h**,[17] **1i**,[1] **1n**,[1] **2a**,[18] **2b**,[19] **2c**,[18] **2d**,[20] **2e**,[11] **2g**,[21] **2h**,[22] **2i**,[23] **2j**,[24] **2k**,[24] **2l**,[24] **2m**,[25] **2n**,[21] **2o**,[6] **2p**,[12] **2q**,[13] **2r**,[14] and **2s**[15] are described in the literature and were fully characterized by their spectral data (^{1}H nmr: Varian EM 360-L; I.R.: Perkin-Elmer 577; M.S.: Varian Mat 311A) and, eventually, by their m.p. (uncorrected, hot-stage microscope).

Elemental analysis of **2f** was performed at the "Station de Haute-Belgique" (Libramont-Chevigny, Belgium).

General procedure[2]

A solution of thionyl chloride (0.9 ml; 12 mmol) in dichloromethane (12 ml) was cooled down to 0° C. Then a solution of pyridine (1.0 ml; 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 kept at 0° C for one hour[16] and formation of the N-(1-chloroalkyl)pyridinium chloride was confirmed (on the basis of reported criteria[16]) by an analysis of the ^{1}H nmr spectrum directly recorded on a sample of the reaction medium. The enaminocarbonyl compound (30 mmol) was then slowly added and stirring at room temperature was maintained overnight (not optimized times[4]). The solvent was evaporated under reduced pressure and the residue was triturated with water to yield the crude final product.

N-(1-Chloro-2-phenylethyl)pyridinium chloride (**1d**; not isolated)
^{1}H nmr (CH_2Cl_2 + DMSO d_6): 9.9 (d; 2H; H^2 and H^6 pyr); 8.9 (t; 1H; H^4 pyr); 8.3 (t; 2H; H^3 and H^5 pyr); 7.8 (t; 1H; CHCl); 7.3 (c; 5H; Ph); 4.0 (dd; 2H; CH_2) ppm.

N-(1-Chloro-2-phenylpropyl)pyridinium chloride (**1f**; not isolated)
^{1}H nmr (CH_2Cl_2 + DMSO d_6): 9.8 (d; 2H; H^2 and H^6 pyr); 9.2 (d; 1H; CHCl); 8.8 (t; 1H; H^4 pyr); 8.2 (t; 2H; H^3 and H^5 pyr); 7.6-7.0 (c; 5H; Ph); 4.2 (m; 1H; CHPh); 1.6 (d; 3H; CH_3) ppm.

N-[Chloro(2-nitrophenyl)methyl]pyridinium chloride (**1j**; not isolated)
^{1}H nmr (CH_2Cl_2 + DMSO d_6): 9.7 (d; 2H; H^2 and H^6 pyr); 8.8 (t+s; 2H; H^4 pyr + CHCl); 8.5-7.8 (c; 6H; H^3 and H^5 pyr + Ar) ppm.

N-[Chloro(3-nitrophenyl)methyl]pyridinium chloride (**1k**; not isolated)
^{1}H nmr (CH_2Cl_2): 9.7 (d; 2H; H^2 and H^6 pyr); 9.1 (s; 1H; CHCl); 8.6-7.3 (c; 7H; H^4 pyr + H^3 and H^5 pyr + Ar) ppm.

N-[Chloro(4-nitrophenyl)methyl]pyridinium chloride (**1l**; not isolated)
^{1}H nmr (CH_2Cl_2): 9.8 (d; 2H; H^2 and H^6 pyr); 9.2 (s; 1H; CHCl); 8.8 (t; 1H; H^4 pyr); 8.3 (t; 2H; H^3 and H^5 pyr); 8.2 (s; 4H; Ar) ppm.

N-[Chloro(4-chlorophenyl)methyl]pyridinium chloride (**1m**; not isolated)
^{1}H nmr (CH_2Cl_2): 9.8 (d; 2H; H^2 and H^6 pyr); 9.2 (s; 1H; CHCl); 8.7 (t; 1H; H^4 pyr); 8.3 (t; 2H; H^3 and H^5 pyr); 7.9 (d; 2H; H^2 and H^6 Ar); 7.4 (d; 2H; H^3 and H^5 Ar) ppm.

N-[Chloro(2-thienyl)methyl]pyridinium chloride (**1o**; not isolated)
^{1}H nmr (CH_2Cl_2): 9.7 (d; 2H; H^2 and H^6 pyr); 9.2 (s; 1H; CHCl); 8.7 (t; 1H; H^4 pyr); 8.2 (t; 2H; H^3 and H^5 pyr); 7.9-7.0 (c; 3H; thienyl) ppm.

Diethyl 1,4-dihydro-2,6-dimethyl-4-(1-phenylethyl)-3,5-pyridine-dicarboxylate (**2f**)
M.p. (CH_3CN): 127-9° C. ^{1}H mr ($CDCl_3$): 7.4 (s; 5H; Ar); 6.8 (br; 1H; NH); 4.2 (c; 4H+1H; $CO_2CH_2CH_3$ + C^4H DHP); 2.5 (c, 1H; Ph-CH); 2.2 (s; 6H; CH_3 2,6); 1.2 (t; 6H; $CO_2CH_2CH_3$); 0.8 (d; 3H; Ph-CH-CH_3) ppm. I.R. (KBr) 3300 (N-H); 1670 (C=0) cm^{-1}.
$C_{21}H_{27}NO_4$ (357.45). Anal.Calcd. : C, 70.56; H, 7.61; N, 3.92.
Found : C, 70.11; H, 7.72; N, 3.97.

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