

AN UNUSUAL AROMATIZATION OF HANTZSCH-TYPE 4-ANTIPYRYL-1,4-DIHYDROPYRIDINES

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Abstract --- Under acidic conditions, Hantzsch-type 4-antipyril-1,4-dihydro-pyridines undergo an elimination of the 4-substituent to yield 4-unsubstituted pyridines and antipyrine. The mechanism and the scope of the reaction are discussed.

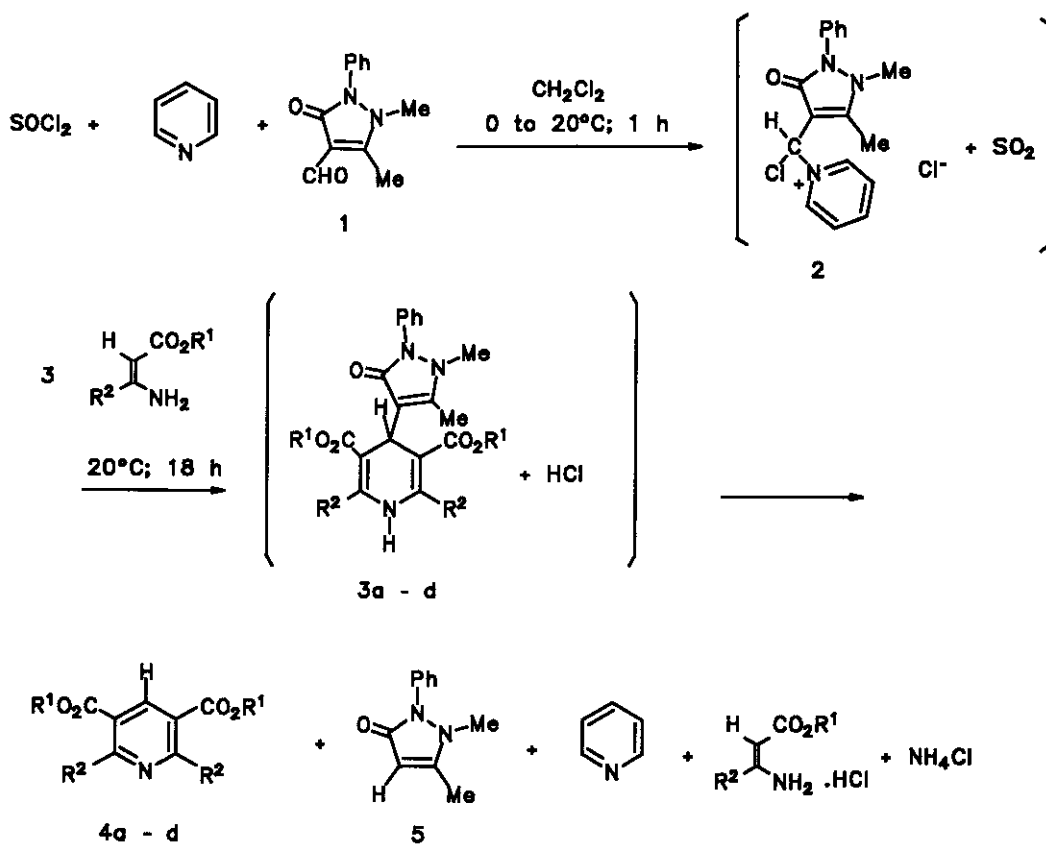
Dedicated to Professor A.R. Katritzky on the occasion of his 65 birthday

Recently we have shown^{1, 2} that *N*-(1-haloalkyl)azinium halides are efficient precursors for the preparation of Hantzsch 1,4-dihydropyridines when they are subjected to reaction with enamincarbonyl derivatives. 2,3-Dihydro-1,5-dimethyl-3-oxo-2-phenyl-1*H*-pyrazole-4-carboxaldehyde (**1**, 4-formyl-antipyrine) was among the aldehydes we used to synthesize the azinium halides. However, in this case we observed the following unusual behavior.

Salt (**2**) was prepared by reaction of aldehyde (**1**) with a mixture of thionyl chloride and pyridine in dichloromethane according to our previously described method.^{3, 4} The salt was not isolated but treated directly with an excess (3 equivalents) of ethyl 3-amino-2-butenate.

The expected compound was the 1,4-dihydropyridine (**3a**) bearing a dihydropyrazole moiety in position 4. Surprisingly, inspection of the spectral data revealed that diethyl 2,6-dimethyl-3,5-pyridine-dicarboxylate (**4a**) was formed in excellent yield (95 % based on **1**). ¹H-Nmr studies also showed unambiguously that other reaction products were 2,3-dihydro-1,5-dimethyl-2-phenyl-1*H*-pyrazol-3-one (**5**, antipyrine), the hydrochloride of the enaminoester, and (free) pyridine. Compounds (**4b - d**) were obtained in the same way (Scheme 1).

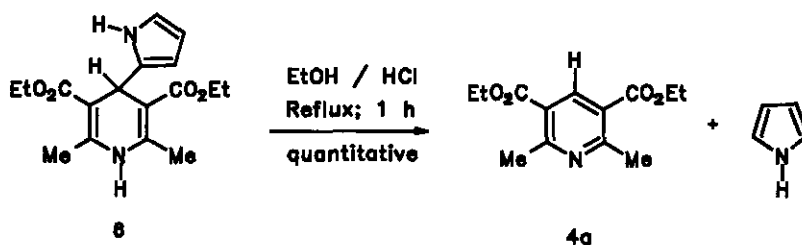
Because dialkyl 2,6-dimethyl-3,5-pyridinedicarboxylates are involved in the metabolism ^{5 - 7} of therapeutic Hantzsch-type 1,4-dihydropyridines, it was of interest to elucidate the mechanism of this new reaction. Although the dihydropyridines (**3**) were not detected (¹H-nmr), they are obligatory intermediates in the formation of **4**. Aromatization of **3** by sulfur dioxide⁸ (evolved during the preparation of salt **2**) can be ruled out as we obtained the same results with an isolated sample of salt (**2**). We then reasoned that hydrochloric acid (evolved during the interaction with the enaminoester) could protonate the dihydropyrazole ring (probably at the C(4)-position due to the particular electronic delocalisation in the enaminone-like moiety⁹), thus creating a good leaving group. This was confirmed by the two following experiments. In a solution of dichloromethane saturated with gaseous hydrochloric acid, a pure sample of **3a** (prepared by a classical Hantzsch reaction¹⁰) disappears readily to yield **4a** and **5**. We also observed that **3a** is stable upon heating in ethanol, but affords **4a** (and **5**) when heated in a mixture of ethanol and hydrochloric acid (10/1).



	R ¹	R ²	Overall yield of 4 based on 1	mp (°C) of 4
a	Et	Me	95 %	70 - 72
b	Me	Me	90 %	47 - 48
a	<i>t</i> -Bu	Me	90 %	142 -143
d	Et	Ph	85 %	70 - 71

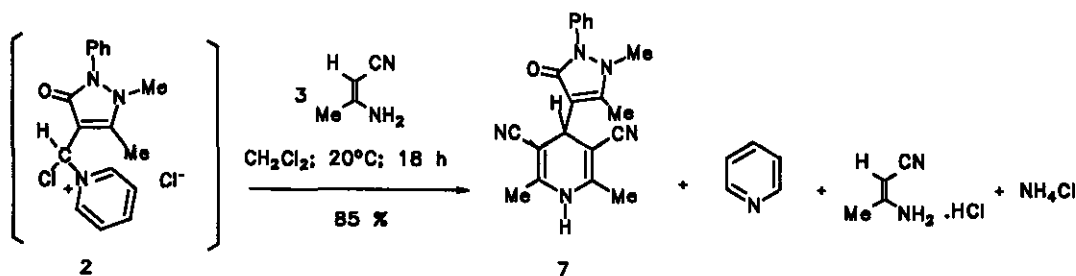
Scheme 1

Under these latter conditions, diethyl 1,4-dihydro-4-(2-pyrrolyl)-3,5-pyridinedicarboxylate (**6**) also undergoes a ready cleavage of the inter-ring bond to afford **4a** and pyrrole (Scheme 2). Thus, it can be foreseen that this unusual aromatization is not restricted to the examples presented in this paper.



Scheme 2

On the other hand, starting from salt (**2**) and 3-amino-2-butenenitrile, we isolated the less hindered 4-antipyril-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarbonitrile (**7** - Scheme 3). No splitting of the antipyril moiety occurred. Therefore, together with the formation of an aromatic pyridine, the driving force for the expulsion of the azole could be the relief of steric interactions¹¹ with the flanking ester groups.



Scheme 3

In conclusion, our procedure for preparing dialkyl 3,5-pyridinedicarboxylates is characterized by its simplicity, by high yields, and by the fact that the azole can be recycled for the preparation of the starting aldehyde.^{12,13} Contrary to most methods¹⁴ that afford similar pyridine derivatives, our route does not require the use of an external oxidant so that it can be employed for selective aromatization of Hantzsch-type 1,4-dihydropyridines without damage to sensitive substituents.

EXPERIMENTAL

Dimethylethyl 3-amino-2-butenolate,¹⁵ ethyl 3-amino-3-phenylpropenoate,¹⁶ and compounds (**4a**,¹⁷ **4b**,¹⁸ **4c**,¹⁹ **6**²⁰) have been described in the literature. All products were fully characterized by their spectral data (¹H-nmr: Varian EM 360-L; ir: Perkin-Elmer 577) and, in most cases, by their melting points (uncorrected; hot-stage microscope).

The elemental analyses were carried out at the Station de Haute-Belgique (Libramont-Chevigny, Belgium).

Preparation of compounds 4 and 7

Aldehyde (**1**) (2.16 g, 10 mmol) was slowly added to a solution of thionyl chloride (0.9 ml, 12 mmol) and pyridine (1.0 ml, 12 mmol) in dichloromethane (10 ml) maintained at 0 °C. The solution was allowed to warm to room temperature for 1 h. Formation of salt (**2**) was confirmed by ¹H-nmr on the basis of known criteria⁴ [2.8 (s, 3H, CH₃); 3.4 (s, 3H, N-CH₃); 7.4(m, 5H, C₆H₅); 8.0 (m, 2H, H³ and H⁵ Pyr); 8.4 (t, J = 8 Hz, 1H, H⁴ Pyr); 8.8 (s, 1H, CHCl); 10.2 (d, J = 5 Hz, 2H, H² and H⁶ Pyr) ppm. Solvent: CH₂Cl₂].

The enaminone derivative (30 mmol) was slowly added and stirring at room temperature was maintained overnight. The solvent was evaporated under reduced pressure and the residue was triturated with water (20 ml) to yield the crude compound.

Preparation of compounds 3a and 6

A mixture of ethyl 3-oxobutanoate (6.45 g, 50 mmol), aldehyde (25 mmol), and concentrated aqueous ammonia (2.5 ml) in ethanol (5 ml) was stirred under reflux for 8 h. After evaporation of the solvents under reduced pressure, the residue was triturated with a mixture (20 ml) of water and ethanol (1/1) to yield the crude compound (70 - 90 %).

Splitting of the azolyl moiety

Method A

Gaseous hydrochloric acid was bubbled in a solution of the dihydropyridine (**3a**) (0.44 g, 1 mmol) in dichloromethane (10 ml) for 5 min. Stirring at room temperature was maintained for 2 h. Evaporation of the solvent yielded a mixture of **4a** and **5**.

Method B

A mixture of the dihydropyridine **3a** or **6** (5 mmol) in ethanol (10 ml) and concentrated hydrochloric acid (1 ml) was heated under reflux for 6 h. Evaporation of the solvents yielded a mixture of **4a** and the corresponding azole.

Diethyl1,4-dihydro-4-(2,3-dihydro-1,5-dimethyl-3-oxo-2-phenyl-1H-pyrazol-4-yl)-2,6-dimethyl-3,5-pyridinedicarboxylate (3a)

mp (EtOH/H₂O - 1/1): 259 - 261 °C.

¹H-Nmr (DMSO d₆): 1.2 (t, J = 7 Hz, 6H, CH₂CH₃); 2.2 (s, 6H, 2-CH₃ and 6-CH₃); 2.3 (s, 3H, CH₃ Pyraz); 3.4 (s, 3H, N-CH₃); 4.1 (q, J = 7 Hz, 4H, OCH₂); 4.7 (s, 1H, H⁴); 7.4 (m, 5H, N-C₆H₅); 8.7 (br, 1H, NH) ppm.

Ir (KBr): 3290, 3220 (N-H); 1680 (C=O, ester); 1639 (C=O) cm⁻¹.

C₂₄H₂₉N₃O₅ (439.51). *Anal.* Calcd : C, 65.59; H, 6.65; N, 9.56. Found: C, 66.00; H, 6.54; N, 9.41.

1,4-Dihydro-4-(2,3-dihydro-1,5-dimethyl-3-oxo-2-phenyl-1H-pyrazol-4-yl)-2,6-dimethyl-3,5-pyridinedicarbonitrile (7)

mp (EtOH/H₂O - 1/1): 289 - 291 °C.

¹H-Nmr (DMSO d₆): 1.9 (s, 6H, 2-CH₃ and 6-CH₃); 2.2 (s, 3H, CH₃ Pyraz); 3.3 (s, 3H, N-CH₃); 4.3 (s, 1H, H⁴); 7.2 - 7.5 (m, 5H, N-C₆H₅); 9.4 (br, 1H, NH) ppm.

Ir (KBr): 3200, 3100 (N-H); 2200 (CN); 1630 (C=O) cm⁻¹.

C₂₀H₁₉N₅O (345.20). *Anal.* Calcd : C, 69.55; H, 5.54; N, 20.28. Found: C, 69.68; H, 5.51; N, 20.12.

Diethyl 2,6-diphenyl-3,5-pyridinedicarboxylate (4d)

The compound was recrystallized from petroleum ether (40 - 60 °C). mp : 70 - 71 °C

¹H-Nmr (CDCl₃): 1.3 (t, J = 7 Hz, 6H, CH₃); 4.3 (q, J = 7 Hz, 4H, OCH₂); 7.2 - 7.6 (m, 10 H, C₆H₅); 8.7 (s, 1H, H⁴) ppm.

Ir (KBr): 1710 (C=O) cm⁻¹.

C₂₃H₂₁NO₄ (375.42). *Anal.* Calcd : C, 73.58; H, 5.61; N, 3.87. Found: C, 73.57; H, 5.54; N, 3.65.

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