Decarbonylation of Some Pyrimidine-5-carboxaldehydes

Thomas J. Delia*, Barry Polenz and Mary C. Martin

Malcolm H. Filson Laboratories, Department of Chemistry, Central Michigan University, Mt. Pleasant, MI 48859

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In the course of determining the ultraviolet spectra of some 2,4,6-trisubstituted-pyrimidine-5-carboxaldehydes we discovered the facile loss of the formyl group. The reaction appears to be restricted to pyrimidine-5-carboxaldehydes containing three strongly electron donating substituents. Loss of the formyl group occurs at room temperature only in methanol with large excess of acid. Other alcohols and water fail to afford the decarbonylated product. A suggested pathway for this reaction is offered.

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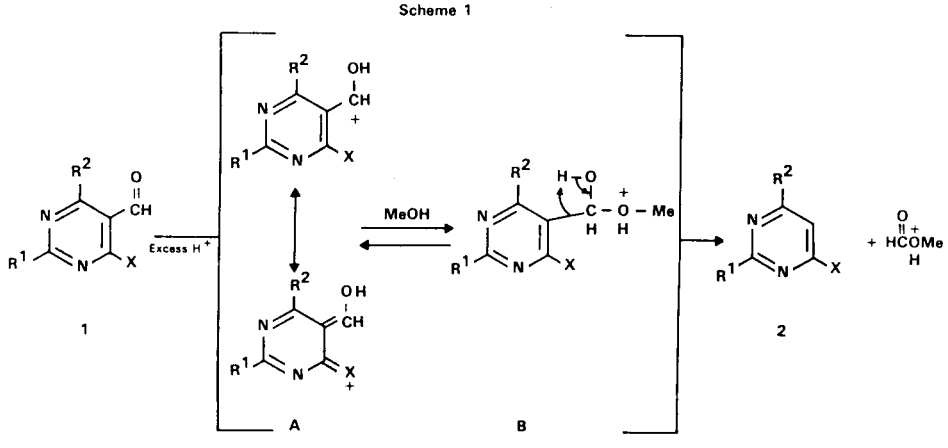
Pyrimidines in general and pyrimidine-5-carboxaldehydes in particular have been the subject of extensive investigation [1]. In the latter case the aldehyde serves as a useful building block for more elaborate groups at position five or for fusing rings onto the original pyrimidine.

We have recently reported the synthesis of some 2,4,6-trisubstituted-pyrimidine-5-carboxaldehydes [2]. In the course of some routine spectral characterization we observed the loss of the aldehyde moiety in some of the derivatives under extremely mild conditions. This report describes the results of our investigation into the scope of this facile reaction.

The decarbonylation of heterocyclic aldehydes has been the subject of few studies, except for the metal-catalyzed decarbonylation of furfural [3]. Decarbonylation reactions utilizing mild catalytic conditions have been much less investigated. Quinoxalinecarboxaldehydes lose the formyl moiety when treated with an unhindered secondary amine [4] and indole aldehydes behave similarly in the presence of a phosphine catalyst [5]. However, only imidazole carboxaldehydes [6] and pyrimidine carboxaldehydes [7] have been reported to lose the aldehyde group as a result of interaction with solvent.

In the latter case the 4-chloro-6-dialkylaminopyrimidine-5-carboxaldehydes resulted in ring opened products when treated with either boiling water or aqueous acid [7]. In a few examples of 4,6-disubstituted-pyrimidine-5-carboxaldehydes treated with either aqueous or ethanolic hydrogen chloride, in which the amount of hydrogen chloride was in excess, simple loss of the aldehyde function occurred. The nature of the substitutents can have a significant effect on the stability of the pyrimidine ring [7]; see references [2] and [3] cited there. The compounds which

Scheme 1



Cmpd	R^1	R^2	X
a	NH_2	NH_2	NH_2
b	NH_2	OH	NH_2
c	OH	OH	NH_2
d	OMe	OMe	OMe

are the subject of this investigation all possess three electron donating groups in addition to the aldehyde moiety.

Results and Discussion.

When 2,4,6-triamino-5-formylpyrimidine, **1a**, was treated with methanolic sulfuric acid at room temperature a gradual change in the uv maximum of the solution occurred. A solution of **1a** in methanol exhibited uv maxima at 235 nm, 255 nm, and 296 nm. Addition of 500 equivalents of sulfuric acid immediately caused a shift to 236 nm, 268 nm (sh), and 280 nm, which gradually changed to 274 nm over a period of two hours. Examination of the solution for longer periods did not significantly alter these results (see Figure 1). At lower mole ratios, for example, 100:1, 60:1, 50:1, and 10:1, the reaction proceeded at a progressively slower rate until no change was observed at a 1:1 ratio. When the solution of acid and **1a** (100:1 ratio) was heated to 40° for several hours a gradual loss of the characteristic uv maxima was observed suggesting decomposition of the ring to open chain products. This observation was not pursued but may be related to earlier work [7].

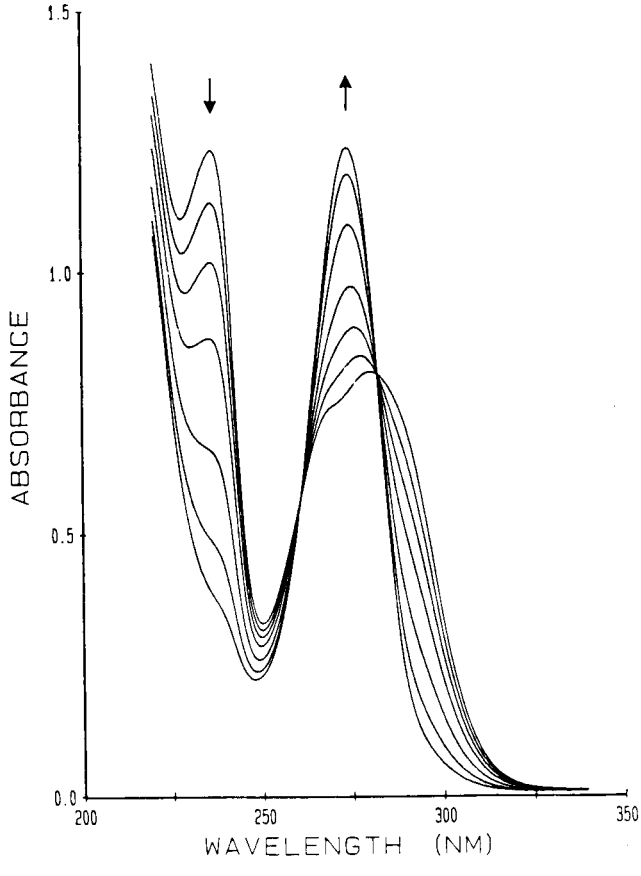


Figure 1. Representative ultraviolet spectra of changes in absorption. Changes in compound **1a** in excess acid over a five hour period.

The reaction at room temperature was scaled up in an effort to obtain sufficient material for identification. The white product collected (see Experimental for details) was determined to be 2,4,6-triaminopyrimidine, **2a**, on the basis of uv, mass spectral and ir comparisons with an authentic sample.

It was of interest to see if this behavior could be observed in other solvents. Solutions of **1a** were prepared in ethanol, 2-propanol and water. Sufficient sulfuric acid was added to each solution to afford molar ratios in excess of 100:1. Apart from an immediate shift in uv maxima upon addition of the acid, due undoubtedly to protonation of the compound, no further changes were observed during periods in excess of nine hours. In the case of the aqueous acid solution of **1a**, after 18 hours sufficient concentrated sodium hydroxide was added to provide a solution with *p*H 12. The original absorption maxima (prior to acid addition) were restored thereby confirming that no decarbonylation to **2a** has occurred.

In each of the solvents used, thin layer chromatography confirmed the results obtained by uv measurements.

Further experimentation was focused on the three additional aldehydes, although only methanol was employed as solvent. In the case of 2,4-diamino-5-formyl-6-oxo-1*H*-pyrimidine, **1b**, the uv maxima changed from 221 nm and 291 nm (without acid) to 243 nm and 286 nm (with acid in a ratio of 800:1). Over a period of 36 hours the maximum slowly changed to 264 nm. Thus, although the results are similar to those for **1a** the rate of decarbonylation is obviously much slower. Again the reaction was repeated on a scale that permitted the isolation of an off-white product. This solid proved to be identical with an authentic sample of **2b** by spectral comparison.

When 4-amino-5-formyl-2,6-dioxo-1*H*,3*H*-pyrimidine, **1c**, was subjected to similar treatment (150:1 ratio of acid to **1c**) a gradual shift in uv maxima occurred over a five hour period, indicating decarbonylation to **2c**.

Finally, 5-formyl-2,4,6-trimethoxypyrimidine, **1d**, was treated with sulfuric acid (ratio of 1000:1). After an initial change in which the uv maximum shifted from 273 nm to 247 nm (immediately upon addition of the acid) no further change was noted even after five days. This reaction was repeated on a larger scale and the white solid obtained, after evaporation of the solvent, proved to be **1d** when compared to an authentic sample. No evidence of a decarbonylated product, **2d**, could be found.

The results of these experiments are summarized in Table 1.

Previous work by Antonini and co-workers [6] reported the decarbonylation of imidazole-2-carboxaldehydes. In their studies it was found that acid to heterocyclic ratios of <1 were necessary to effect loss of the aldehyde moiety. In fact, ratios >1 provided the acetals. Our results are in

Table 1

Decarbonylation Reaction Conditions and Results

Compound	Solvent	Acid/Compound Ratio	Time [a]	λ max (nm) Initial	Final
1a	MeOH	500:1	5	236, 280	274
1a	EtOH	1000:1	15	236, 266, 286	236, 266, 286
1a	2-PrOH	1000:1	13	235, 268, 282	235, 268, 282
1a	H_2O	*p*H 2	24	234, 264, 284	234, 264, 284
1b	MeOH	800:1	36	243, 286	264
1c	MeOH	1500:1	5	243, 284	263
1d	MeOH	1000:1	4	247	247

[a] All values are in hours and the period of time reflects the point at which no further observable changes occurred.

direct contrast to the behavior exhibited by the imidazole carboxaldehydes. This may be explained by the fact that imidazoles are π-excessive ring systems while pyrimidines are π-deficient. Hence, considerably greater acidity is needed in the case of pyrimidines to activate the carbonyl group toward nucleophilic agents, such as methanol.

A pathway depicting a reasonable process in shown in Scheme 1. It is essential that protonation of the carbonyl group occur. Intermediate **A** represents the minimum requirements for the reaction. That compounds **1a-c** undergo the decarbonylation reaction and **1d** does not suggests a contribution from substituent X which stabilizes that protonated aldehyde. Clearly the amino group has greater capacity to do this than the methoxy group. Furthermore, **1a**, with two adjacent amino groups, is much more effective at this than either **1b** or **1c** and, hence, a faster rate of decarbonylation is observed.

None of these pyrimidines is a particularly strong base yet there is the likelihood that the intermediate **A** may be a dication is some instances. Compound **1a**, with an estimated pK_a of 4.5 most certainly would be essentially in a dication form while **1b**, with a pK_a of approximately 1.1, is more likely to be *ca.* 50% in the dication state under the experimental conditions. It is not clear that the presence of or absence of protonation on a ring nitrogen substantially affects the results. For, in **1c** and **1d**, with estimated pK_a values of -1.0, only **1c** undergoes the decarbonylation reaction. Both of these structures would be protonated on ring nitrogen to the extent of perhaps 1%.

Further reaction of intermediate **A** with solvent leads to the tetrahedral intermediate **B**. The postulated structures clearly represent the first steps in hemiacetal formation, with all of the susceptibilities to steric and electronic effects associated with that process. The most reasonable explanation for the success of methanol and the failure of ethanol or 2-propanol in this process is a steric one. The protonated hemiacetal at position 5 is flanked by two groups, R^2 and X, which create a crowded environment. The smaller alcohol, methanol, is better able to fit into this restricted environment. Subsequent electron migrations, as shown, afford **2a-c** and protonated methyl formate.

Finally, the failure of water to participate in the decarbonylation reaction cannot be attributed to steric considerations. Rather the tetrahedral intermediate, **B**, in this case would be a hydrate, a very unstable structure due both to steric and electronic factors. Hence, it is not likely that any significant amount of the hydrate could be present due to an equilibrium which must surely favor **A** and no reaction is observed.

These observations should alert other investigators to pay careful attention to the conditions of reactions involving these and similar pyrimidine carboxaldehydes.

EXPERIMENTAL

Ultraviolet spectra were recorded on a Varian 2300 spectrophotometer using matched 1 cm quartz cells. The solvents used were hplc grade methanol, reagent grade 95% ethanol and 2-propanol, distilled, deionized water, and concentrated sulfuric acid.

Infrared spectra were obtained using a Perkin Elmer 597 grating spectrophotometer and mass spectra were measured on a Hewlett Packard 5995A GC/MS instrument, using a direct insertion probe. Thin layer chromatography was carried out on silica gel plates using methanol, methanol:ethyl (8:2) or ethyl acetate as eluting solvents.

General Procedure.

Stock solutions for all pyrimidines were prepared in the following way. Approximately 0.1000 g of each pyrimidine was weighed into a 10 ml volumetric flask and diluted to the mark with the appropriate solvent. After shaking vigorously the mixtures were allowed to stand for several hours. The liquid was decanted from undissolved pyrimidine; **1d** dissolved completely. The solid residues were dried thoroughly and weighed. Concentrations were based on the dissolved quantities.

Stock solutions for sulfuric acid were prepared by dissolving weighed amounts (0.04-0.17 g) of the acid in either 10 ml or 25 ml volumetric flasks containing the appropriate solvents.

Dilutions were made of these stock solutions to achieve suitable concentrations for uv examination and to provide specific ratios of acid to pyrimidine.

In general, sample solutions were prepared from 2.4 ml of the acid solution and 10-300 μl of the pyrimidine solution. Mixing of the two solutions, placement of the cell in the spectrometer and the first recording were usually carried out in less than two minutes. All recordings covered the range of 340-215 nm.

Isolation Procedure.

A sample of the appropriate aldehyde (*ca.* 100 mg), methanol (25 ml) and concentrated sulfuric acid (0.1 ml) were placed in a 50 ml round bottom flask and stirred at room temperature for 3 days. A solid resulted either by precipitation from the reaction mixture or after evaporation of the solvent. After thorough drying the product was examined by tlc, ir, uv and mass spectra. By comparison with authentic samples it was confirmed that **2a** (from **1a**), **2b** (from **1b**), **2c** (from **1c**) and **1d** were isolated.

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REFERENCES AND NOTES

[1] D. J. Brown, "The Pyrimidines", Interscience, New York, 1962, and Supplements I and II.

[2] T. J. Delia and R. Otteman, *Heterocycles*, **20**, 1805 (1983).

[3] P. Lejemble, P. Kalck, Y. Maire and A. Gaset, *Top. Furan Chem., Proc. Symp. Furan Chem.*, 4th, 1983, p 175; *Chem. Abstr.*, **101**, 210871q (1984); G. Gardos and A. Redey, *Hung. J. Ind. Chem.*, **7**, 423 (1979); Z. Dudzik, R. Sawala and Z. Szuba, Polish Patent 95,215 (1978); *Chem. Abstr.*, **90**, 87249t (1979); A. Avots, A. Karmil'chik, V. Stonkus, V. Aizbalts, M. V. Shymanskaya and S. Hillers, *Latv. PSR Zinat. Akad. Vestis, Kim. Ser.*, 233 (1975); *Chem. Abstr.*, **83**, 78991g (1975); A. Ya. Karmil'chik, V. Stonkus and S. Hillers, *Geterogennyi Katal. Reakts. Poluch. Prevrashch. Geterotsikl. Soedin.*, 61 (1971); *Chem. Abstr.*, **76**, 126683n (1972).

[4] R. F. Meyers, U. S. Patent 3,974,438 (1976); *Chem. Abstr.*, **85**, 21464z (1976).

[5] M. D. Meyer and L. I. Kruse, *J. Org. Chem.*, **49**, 3195 (1984).

[6] I. Antonini, G. Cristalli, P. Franchetti, M. Grifantin, Y. Gulini and S. Martelli, *J. Heterocyclic Chem.*, **15**, 1201 (1978).

[7] J. Clark, B. Parvizi and I. W. Southon, *J. Chem. Soc., Perkin Trans. I* 125 (1976).