Synthesis of Schiff Bases Derived from 2,4,6-Trimethoxypyrimidine-5-carboxaldehyde

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Schiff bases have been formed with methyl-, methoxy-, nitro- and unsubstituted anilines and 2,4,6-trimethoxypyrimidine-5-carboxaldehyde.

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In a previous report we described our initial work on the formation of 5-aminosubstituted pyrimidine derivatives (2). We wished to extend these investigations to other pyrimidine derivatives and, among others, explored the Mannich reaction with 2,4,6-trimethoxypyrimidine (**1**). Treatment of **1** with butylamine and paraformaldehyde failed to provide the desired 5-butylaminomethyl-2,4,6-trimethoxypyrimidine (**2**).

This failure prompted us to investigate alternate methods for the introduction of the -C-N- functionality at position 5. A review of the literature indicated that 2,4,6-trimethoxypyrimidine-5-carboxaldehyde (**3**) might serve as a useful intermediate for our purpose. Further, the literature indicated that very little has been reported with 2,4,6-trisubstitutedpyrimidine-5-carboxaldehydes (3a-d).

The use of a variety of aromatic amines in such reactions also seemed to be limited (3). Of these reports only the work of Grundmann and Richter (3d) appeared to involve **3**. In a related report Stogryn (4) employed 2,4-dimethoxypyrimidine-5-carboxaldehyde as an intermediate for the synthesis of 5-substitutedmethyl pyrimidine derivatives.

The sequence of reactions employed in this investigation is described in Figure 1. Among the many methods for the introduction of the formyl group into aromatic compounds the Vilsmeier-Haack reaction appeared to be most suitable for use with heteroaromatic ring systems. The method of Grundmann and Richter was adapted with only slight modification (3d). Treatment of **1** with DMF-phosphoryl chloride at 0°, followed by heating to 50° for 1 hour and hydrolysis with ice and water, gave **3** in 65% yield. The product was sufficiently pure for further reactions and was characterized by ^{1}H pmr and melting point comparison with the reported literature value (3d).

Schiff base formation involves the nucleophilic attack of an amine on the carbonyl carbon of the aldehyde function as the rate-determining step. Thus electronic and steric factors of the amine would be expected to play a significant role in the success of the reaction. Indeed this was found to be the case.

When a mixture of **3** and the corresponding anilines in absolute ethanol was heated to reflux for periods in excess of 24 hours compounds **4a-g** were obtained, after work up, in 50-85% crude yield. Subsequent purification to achieve analytical samples reduced these figures to 20-40%. Figure 1. lists the data for the products (**4**) derived from this reaction. In all successful cases substituents were limited to meta and para positions. No trends, based on the various electronic effects of the substituents were observed. And we were pleased to find that the strongly electron withdrawing nitro group presented no real obstacles in this reaction (5). Structural assignments were supported by elemental analysis and ^{1}H pmr spectra. Only the values for the imino-H (H_7) and the methoxyl groups are reported in the figure.

Noteworthy is the fact that the 2-chloro-, 2-nitro-, 2-methoxy-, and 2-aminoanilines did not result in the desired products. Thus a variety of electronic influences appeared to have little effect when positioned ortho to the amino group. Due to the poor reactivity in these cases the reaction mixture was treated more vigorously than in the successful cases. Some very high melting compounds (>300°) were obtained which could not be purified sufficiently for characterization. However, ^{1}H pmr spectra indicated the absence of the methoxy grouping. Until these products can be examined more critically we have speculated that hydrolysis to barbituric acid derivatives (6) followed by subsequent reactions is the most likely explanation for these impure products.

EXPERIMENTAL

Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN. Melting points were recorded on a Fisher-Johns melting point apparatus and are uncorrected. ^{1}H pmr spectra were recorded on a Varian model T-60 in deuteriochloroform with tetramethylsilane as the internal standard. Tlc analyses were performed on silica gel plates using methanol as the eluent.

Preparation of 2,4,6-Trichloropyrimidine.

This compound was prepared from barbituric acid according

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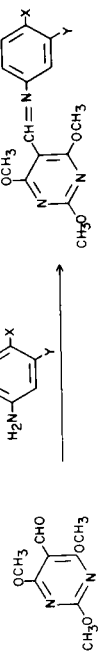
Figure 1



3

4

CMPD	Substituents		Yield %	M.p.	^{1}H pmr -H$_7$	^{1}H pmr -OCH$_3$	Formula	Analyses Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
4a	X = H	Y = H	80	110-112 (a)	8.5	4.1	$C_{14}H_{15}N_3O_3$	61.54	5.49	15.38	61.46	5.50	15.35
4b	X = CH_3O	Y = H	79	124-125 (b)	8.6	4.1	$C_{15}H_{17}N_3O_4$	59.41	5.61	13.86	59.19	5.58	13.74
4c	X = H	Y = CH_3	82	96-98 (b)	8.6	4.1	$C_{15}H_{17}N_3O_3$	62.72	5.92	14.63	62.52	6.07	14.47
4d	X = CH_3	Y = H	77	109-111 (c)	8.6	4.1	$C_{15}H_{17}N_3O_3$	62.72	5.92	14.63	62.71	6.04	14.73
4e	X = H	Y = NO_2	85	191-192 (d)	9.2	3.8	$C_{14}H_{14}N_4O_5$	52.80	4.40	17.60	52.86	4.18	17.65
4f	X = NO_2	Y = H	50	208-210 (d)	8.5	3.8	$C_{14}H_{14}N_4O_5$	52.80	4.40	17.60	52.88	4.22	17.85

(a) Recrystallization solvent = benzene. (b) Recrystallization solvent = butyl acetate. (c) Recrystallization solvent = ligroin (63-75°). (d) Recrystallization solvent = ethyl ether.

to the procedure of Bredereck, *et al.* (5). Sixty g. (82%) of product, b.p. 102°/18 mm, were obtained in this manner.

Preparation of 2,4,6-Trimethoxypyrimidine (**1**).

This compound was prepared from 2,4,6-trichloropyrimidine according to the method of Fisher and Johnson (6), in 78% yield, m.p. 51-52° [lit. m.p. 57° (6)].

Preparation of 2,4,6-Trimethoxypyrimidine-5-carboxaldehyde (**3**).

This compound was prepared essentially according to the method of Grundmann and Richter (3d). Filtration of the product immediately after precipitation should be performed since decomposition occurs readily upon standing. Compound **2** was obtained in 65% yield of sufficient purity to be used directly; m.p. 138-139° [lit. m.p. 137° (3d)].

Preparation of Schiff Bases.

The aldehyde (**3**) (2.5 g., 0.013 mole) was dissolved in hot absolute ethanol (20 ml.) and equimolar amounts of the corresponding anilines, dissolved in a minimum volume of ethanol, were added. The mixture was heated to reflux for periods of 24-36 hours. At the end of this period the mixture was allowed to cool, diluted with water and extracted with ~200 ml. of ether (4 x 50 ml. portions). The ether solution was dried over magnesium sulfate, evaporated under vacuum, and the residue recrystallized from appropriate solvents (see figure). All compounds were either dried in an Abderhalden apparatus or sublimed (**3e,f**) prior to elemental analysis.

REFERENCES AND NOTES

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(5) In the previous investigation (2) the use of nitroaniline in the Mannich reaction did not yield the desired product.

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