Novel Pyrimidine Rearrangement Reaction.[1,2] A New Synthesis of 4-Formylimidazoles

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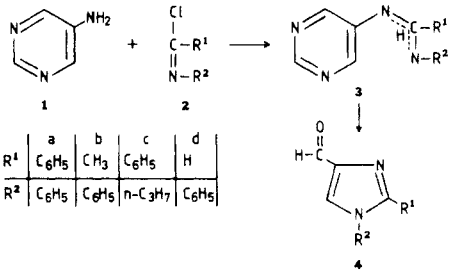
5-Aminopyrimidine gives, on mild heating with *N*-alkyl(aryl)imidoyl chlorides in the presence of phosphorus oxychloride, 4-formyl-1,2-dialkyl(aryl)imidazoles together with the *N*-(pyrimidin-5-yl)-*N*-alkyl(aryl)amidines. It was found that these amidines are the precursors of the imidazoles. This new rearrangement reaction of the pyrimidine ring takes place by attack of the nucleophilic end of the side chain at position 5 of the pyrimidine ring on C(6).

There is convincing evidence that pyrimidines easily undergo ring transformation on treatment with amidines.[3] *N*-Methylpyrimidinium iodide gives with benzamidine 2-phenylpyrimidine and with pivalamidine 2-*tert*-butylpyrimidine. It was proven[3] by ^{15}N labeling that this conversion can be described as an overall replacement of the three-atom fragment N(1)–C(2)–N(3) of the pyrimidine ring by the N–C–N fragment of the amidine. The reaction is initiated by attack of the nitrogen of the amidine on C(6) of the pyrimidinium ring followed by ring opening of the intermediate 1(3),6-dihydropyrimidine and a final recyclization of the open-chain intermediate.

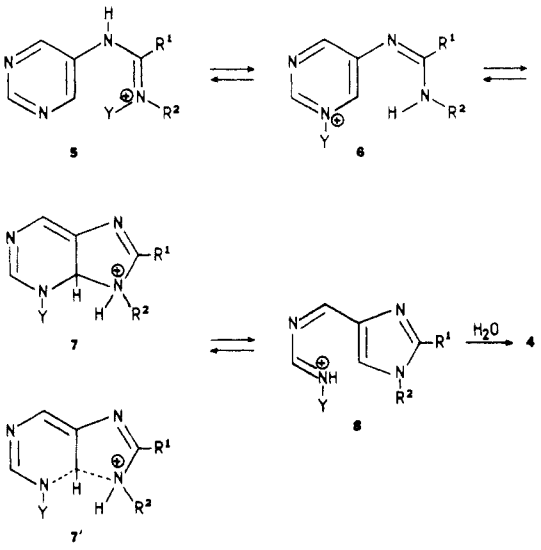
The facile addition of amidines to C(6) of the pyrimidine ring induced us to prepare *N*-(5-pyrimidinyl)-*N'*-alkyl(aryl)amidines (**3**) and to study whether these compounds will rearrange into 1,2,4-trisubstituted imidazoles containing a functional group at position 4 (Schemes I and II).

N-(5-Pyrimidinyl)-*N'*-phenylbenzamidine (**3a**) was prepared by refluxing a solution of 5-aminopyrimidine (**1**) in tetrachloroethylene with purified N-phenylbenzimidoyl chloride[4] (**2a**) for 6 h. After evaporation of the solvent, a dark colored tar remained, and after treatment with water and workup of the reaction mixture (see Experimental Section), amidine **3a** could be isolated. However, besides **3a** and benzamide, a compound ($C_{16}H_{12}N_2O$) was isolated (25.1%) which was assigned the structure of 1,2-diphenyl-4-formylimidazole (**4a**). This structure assignment was based on the following: (i) the ^1H NMR spectrum, which showed besides the phenyl multiplets, sharp singlets at δ 9.83 (HC=O) and at δ 7.70 (the imidazole ring hydrogen); (ii) the IR spectrum, which confirmed the presence of the formyl group [1698 (C=O), 2820, 2743 cm^{-1} (HC=O)]; (iii) an X-ray crystal structure determination (see Figure 1). As seen from Table I the yields of products **3a** and **4a** are low. Lowering the temperature of the reaction or changing the solvent from tetrachloroethylene to chloroform was found to decrease the yields. We observed that by heating of purified **3a** in tetrachloroethylene, no conversion into **4a** took place but that in the presence of phosphorus oxychloride **3a** gave **4a** in nearly quantitative yield. The ease with which this rearrangement reaction occurs induced us to investigate the general scope of the reaction. Therefore 5-aminopyrimidine (**1**) was reacted with some imidoyl chlorides containing different substituents, R^1 and R^2 (**2b,c**). The imidoyl chlorides were prepared by reacting 1 equiv of the corresponding amides with 1 equiv of phosphorus pentachloride. After evaporation of the phosphorus oxychloride, the crude imidoyl chloride was dissolved in tetrachloroethylene and refluxed with **1**. The reaction of **2c** with **1** only yielded the amidine **3c**. However, when **3c** was heated in the presence of phosphorus oxychloride in the same solvent for 5 h, the imidazole **4c** is formed. The yield is considerably lower than that in the reaction of **1** with **2a** (see Table I). When chloroform was used instead of tetrachloroethylene, no imidazole **4c** was formed. The reaction of **2b** with **1** gave a similar result (see Table I). However, chloroform was found to be a better solvent for this reaction since extensive decomposition took place in boiling tetrachloroethylene.

Scheme I



Scheme II



(1) Part 22 in the series of "Ring Transformation of Heterocyclic Compounds with Weak Nucleophiles". For part 21, see P. Barczynski and H. C. van der Plas, *Recl. Trav. Chim. Pays-Bas*, **97**, 256 (1978).

(2) Part 83 on pyrimidines from this laboratory. For part 82, see R. E. van der Stoel, H. C. van der Plas, and G. Geurtsen, *J. Heterocycl. Chem.*, in press.

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(5) Compare for example the pK_a of benzamidine (=11.2) and the pk_a of 5-aminopyrimidine (=2.8).

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Table I. Yields in the Reaction of 1 with the Imidoyl Chlorides (2) and Physical Data of the Compounds 3a-d and 4a-c

compd	substituent R¹	substituent R²	formula	mp, °C (solvent for cryst)	yield, %	microanal data	C	H	exact mass measurements at molecular peak, m/e theor	exptl
3a	C_6H_5	C_6H_5	$C_{17}H_{14}N_4$	151-152 (petroleum ether-ethyl acetate, 8:2)	10.4	calcd found	74.43 74.33	5.14 5.21	274.1218	274.1222
4a	C_6H_5	C_6H_5	$C_{16}H_{12}N_2O$	121-123 (petroleum ether-ethyl acetate, 8:2)	25.1	calcd found	77.40 77.33	4.87 4.91	248.0950	248.0951
3b	CH_3	C_6H_5	$C_{12}H_{12}N_4$	162-163 (ethyl acetate)	9.6	calcd found	67.90 67.80	5.70 5.77	212.1062	212.1067
4b	CH_3	C_6H_5	$C_{11}H_{10}N_2O$	97-100 (ethyl acetate)	10.1	calcd found	70.95 70.98	5.45 5.36	186.0793	186.0791
3c	C_6H_5	n-C_3H_7	$C_{14}H_{16}N_4$	126-126.5 (ethyl acetate)	7.1	calcd found	69.97 69.76	6.71 6.71	240.1374	240.1375
4c	C_6H_5	n-C_3H_7	$C_{13}H_{14}N_2O$	51-52 (petroleum ether)	9.3	calcd found	72.87 72.90	6.59 6.53	214.1106	214.1109
3d	H	C_6H_5	$C_{11}H_{10}N_4$	161-162 (ethyl acetate)	35.3	calcd found	66.63 66.66	5.09 5.12	198.0905	198.0907

Table II. Chemical Shifts (δ) of the Hydrogens in the Compounds 3 and 4 (Solvent $CDCl_3$)

	substituent R¹	substituent R²	compd 3 H-2	H-4,6	R¹	R²	compd 4 HC=O	H-2	R¹	R²
a	C_6H_5	C_6H_5	8.47	8.04		6.7-7.7	9.85	7.71		6.8-7.6
b	CH_3	C_6H_5	8.80	8.49	7.1-7.7	2.05	9.85	7.63	7.1-7.7	2.37
c	C_6H_5	n-C_3H_7	8.45	7.88	7.0-7.3	1.01, 1.70, 3.45	9.77	7.61	7.3-7.6	0.88, 1.73, 3.97
d[a]	H	C_6H_5	8.78	8.58	8.31	7.2-7.5				

[a] Solvent Me_2SO.

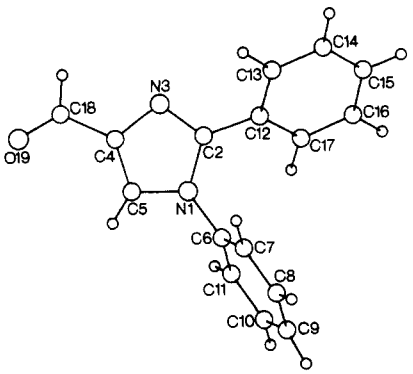

Figure 1. Projection of molecule A onto the plane of the imidazole ring.

The essential role of phosphorus oxychloride in the ring interconversion is certainly due to its property to act as quaternizing agent. The amidine side chain is more basic than the nitrogen of the pyrimidine ring[6] and therefore is more easily quaternized. An equilibrium between the side-chain quaternized species (**5**) and the pyrimidine ring quaternized species (**6**) can be suggested. However, in **5** the nitrogen of the amidine side chain has a decreased reactivity in nucleophilic reactions, while in **6** the pyrimidinium ring—especially position 4 (or 6)—is highly activated for nucleophilic attack by the amidine side chain. Although present in low concentration, **6** is very probably the most reactive species. After the six-membered ring opens, the imidazole derivative **8**, containing the (formimidoylimino)methyl group as a side chain, is obtained. During the workup (see Experimental Section) the side chain is hydrolytically converted into a formyl group. It still is an open question whether the formation of **8** occurs via the bicyclic intermediate **7** or takes place by an attack of the side-chain nitrogen with simultaneous opening of the C(6)–N(1) bond (see **7'**). Recent kinetic data on the ring transformation[6] of 1,2,4-oxadiazoles into 3-aminopyrazolines by primary amines support the occurrence of a process in which the ring forming and ring opening are simultaneous. Attempts to isolate the bicyclic intermediate **7** were unsuccesful.

Rearrangement reactions in which a two-carbon fragment [C(5)–NC(6)] of the pyrimidine ring is actualy involved in the formation of a new five-membered heterocycle are scarce. The rearrangement of 5-acetyl- and 5-formylpyrimidines into pyrazoles[7,8] and isoxazoles,[8] reported to occur on treatment with hydrazine or hydroxylamine, are the sole examples. The reaction described in this paper is a new example of this type of rearrangement. It provides us with a new preparation of 4-formylimidazoles and forms a useful extension of the more classical method of oxidation of 4-(hydroxymethyl)-imidazoles,[9] certainly in those cases where oxidation cannot be applied if substituents vulnerable to oxidizing agents are present.

We also attempted the rearrangement of *N*-phenyl-*N'*-(5-pyrimidinyl)formamidine (**3d**) prepared from **1** and ethyl *N*-phenylformimidate[10] in the presence of phosphorus oxychloride. We observed only the formation of 5-aminopyrimidine and 5-formamidinopyrimidine.[11]

The position of the formyl group in the reaction product of **3a** with phosphorus oxychloride has been proved unequivocally by an X-ray structure determination.[12]

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(12) We gratefully acknowledged the help of G. J. Olthof and P. F. A. B. Seignette of the Laboratory of Crystallography of the University of Amsterdam for the X-ray structure analysis. A more detailed description of the crystallographic structure determination will be published elsewhere.

Crystals of the title compound are triclinic with space group $P\bar{1}$ and four molecules in a unit cell of the following dimensions: a = 10.032 (1) Å, b = 11.076 (1) Å, c = 11.993 (1) Å, α = 74.78 (1)°, β = 96.90 (1)°, γ = 94.58 (1)°. This means that two molecules (A and B) are present in the asymmetric unit. Figure 1 represents a projection of molecule A onto the plane of the imidazole ring. The two molecules A and B in the asymmetric unit are very similar, only small differences being observed in the angles between the rings. The rings are planar within the limits accuracy. In both molecules C(6) is tilted out of the plane of the imidazole ring (0.19 and 0.12 Å in molecules A and B, respectively). The formyl groups at C(4) are practically coplanar with the imidazole rings. Coplanarity of the benzene rings with the imidazole ring is sterically impossible. In both molecules the benzene rings adopt similar positions with a large angle (75° and 69° in molecules A and B, respectively) between the imidazole ring and the benzene ring attached to N(1) and a smaller angle (41° and 32° for molecules A and B, respectively) between the imidazole ring and the benzene ring attached to C(2).

Experimental Section

Melting points are uncorrected. The ^{1}H NMR spectra were recorded on a Hitachi Perkin-Elmer R-24B apparatus with Me_4Si as internal standard. Infrared spectra were taken on a Perkin-Elmer 237 spectrometer in KBr. The mass spectra were performed on AE MS 902 mass spectrometer.

(1) Reaction of 5-Aminopyrimidine (1) with *N*-Phenylbenzimidoyl Chloride (2a). To a boiling solution of 540 mg (2.5 mmol) of *N*-phenylbenzimidoyl chloride (**2a**) in 25 mL of tetrachloroethylene was added 475 mg (5 mmol) of **1**. After the mixture was refluxed for 6 h, the solvent was evaporated off. The solution was made alkaline with aqueous ammonia and then extracted with chloroform. After the extract was dried over anhydrous $MgSO_4$, the solvent was evaporated off, and the crude mixture was separated by column chromatography using petroleum ether/ethyl acetate (7:3) as eluent. For the yields of the products **3a** and **4a**, see Table I. The physical data of those compounds are collected in Tables I and II.

(2) Reaction of 5-Aminopyrimidine (1) with Imidoyl Chloride (2c). Compound **2c** was prepared by refluxing a solution of 2.5 mmol of *n*-propylbenzamidine in 25 mL of chloroform with 524 mg (2.5 mmol) of phosphorus pentachloride for 1.5 h. Then the solvent was evaporated, and the residue (crude **2c**) was dissolved in 25 mL of tetrachloroethylene. A 175-mg (5 mmol) sample of **1** was added. After this solution was refluxed for 1 h, a few drops of the phosphorus oxychloride were added, and refluxing was continued for another 5 h. The solvent was evaporated, and the residue was worked up as described in section 1. The yields and physical data of the compounds obtained are collected in Tables I and II.

(3) Reaction of 5-Aminopyrimidine (1) with Imidoyl Chloride (2b). This reaction was carried out in the same manner as described in section 2. *N*-Phenylacetamide was used as the starting material for preparing **2b**, and chloroform was used as solvent.

(4) Preparation of *N*-Phenyl-*N'*-(5-pyrimidinyl)formamidine (3d). A 745-mg (5 mmol) sample of ethyl *N*-phenylformimidate[11] was heated with 475 mg (5 mmole) of 5-aminopyrimidine (**1**) at 170 °C for 3 h. The solid obtained was purified by column chromatography using ethyl acetate/methanol (9:1) as solvent.

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Registry No. **1**, 591-55-9; **2a**, 4903-36-0; **2b**, 874-69-1; **2c**, 39887-75-7; **2d**, 60566-41-8; **3a**, 75378-57-3; **3b**, 75378-58-4; **3c**, 75378-59-5; **3d**, 75378-60-8; **4a**, 75378-61-9; **4b**, 75378-62-0; **4c**, 75378-63-1; *n*-propylbenzamidine, 22286-00-6; *N*-phenylacetamide, 103-84-4; ethyl *N*-phenylformimidate, 6780-49-0.

Is Oxygen Abstraction by Nucleophilic Reagents a Characteristic Reaction of Oxaziridines?[1]

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The reaction of oxaziridines with nucleophilic reagents was studied. The summarized results are as follows. (1) The nucleophilic reactions occur preferentially on the nitrogen atom and the oxaziridine decomposes into a carbonyl compound and an ylide. (2) The reaction site shifts from nitrogen toward oxygen as the bulk of the ring substituents increases. (3) Cis isomers show faster reaction than trans isomers. (4) The carbon atom of the oxaziridine ring is completely inert to nucleophilic reagents.

Oxaziridines are very unique three-membered heterocyclic compounds constructed of three kinds of atoms having different electronegativities in adjacent positions. The reactions of oxaziridines with amines or sulfides are probably very important for elucidating the characteristic biological properties of oxaziridines based on comparison with that of analogous compounds such as aziridines or oxiranes. Although electrophilic reactions of oxaziridines have been extensively studied and N-protonation has been suggested as the preferred reaction path according to experimental and computational data,[2] a more attractive problem involving the nucleophilic reactions of oxaziridines was obscure until recently. The reactions of brucine or triphenylphosphine with oxaziridines were reported by Emmons[3a] and Horner[4] as early examples of oxygen abstraction from oxaziridines. The former example has been reexamined recently[3b] and appears actually not to involve

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