Recyclization of pyrimidine-2(1*H*)-one into 5-ureido-1,2-azolines

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Abstract

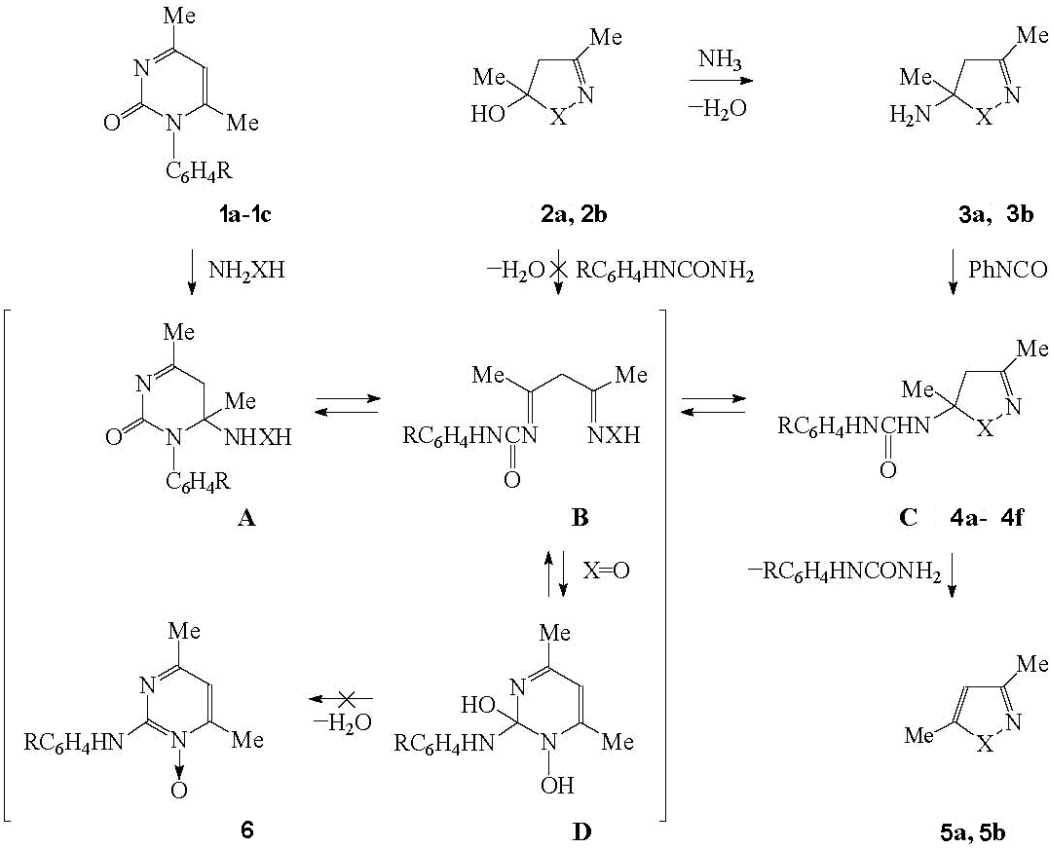
A reaction of 1-aryl-4,6-dimethylpyrimidine-2(1*H*)-ones with hydroxylamine and acetylhydrazine leads to previously unknown 5-*N*-arylcarbamoylamino derivatives of 3,5-dimethyl-Δ^2-isoxa-zoline and -Δ^2-pyrazoline. The structure of the compounds obtained was confirmed by ^{1}H and ^{13}C NMR as well as independent synthesis by reacting phenyl isocyanate with 5-amino-3,5-dimethyl-Δ^2-isoxazoline and -1-acetyl-Δ^2-pyrazoline.

Keywords: Pyrimidine-2-ones, hydroxylamine, 5-ureido-1,2-azolines

Introduction

1,3-*N*-Carbamoylimine oximes (hydrazones) attract attention as potential isomeric (tautomeric) systems capable of existing in both a five-membered 1,2-azoline (Δ^2-iso-xazoline or Δ^2-pyrazoline) form and six-membered pyrimidine-2(1*H*)-one (or -thione) form. We showed previously [1] that these compounds were obtained by combining phenyl isothiocyanate with 5-amino-Δ^2-isoxazolines and 1-acetyl-5-amino-Δ^2-pyrazo-lines. An attempt to prepare them by an alternative route, the reaction of hydroxylamine with pyrimidine-2(1*H*)-thiones, led to the derivatives of pyrimidine 1-*N*-oxides by Dimroth rearrangement.

On the other hand, Kashima *et al.* [2] and Dickinson *et al.* [3] showed that 1,4,6-trisubstituted pyrimidines-2(1*H*)-ones tend to recyclize into isoxazole and pyrazole derivatives when treated with hydroxylamine and hydrazine, respectively; this indicates that the reaction proceeded by the S_N (ANRORC) (Addition-Nucleophile-Ring Opening Ring Closure process) mechanism [4], that is, through intermediate formation of 1,3-*N*-carbamoylimine oximes (hydrazones).Therefore, we reexamined the reaction of hyd-roxylamine and acetylhydrazine with a series of 1-aryl-4,6-dimethylpyrimidine-2(1*H*)-ones (see Scheme).



Scheme 1,4. X=O, **a** R=H, **b** R=4-Me, **c** R=4-MeO, X=NCOMe, **d** R=H, **e** R=4-Me, **f** R=4-MeO;
Scheme 2,3,5. a X=O, **b** X=NCOMe

The reaction of these compounds in methanol was found to proceed at ambient temperature in the presence of sodium hydroxide (see Experimental) to give compounds **4a-4f** in good yield. According to elemental analysis data (Table 1), the composition of compounds **4a-4c** confirmed them as the 1:1 products of hydroxylamine addition to the corresponding pyrimidine-2(1*H*)-ones **1a-1c** and excluded a reaction course by the Dimroth rearrangement [1,2,5] to produce 2-arylamino-4,6-dimethylpyrimidine 1-*N*-oxides **6**. We were unable to prepare compounds **4a-4f** by another possible method: combining N-arylureas with previously described [6,7] 5-hydroxy-3,5-dimethyl-Δ^2-isoxazoline **2a** and 1-acetyl-Δ^2-pyrazoline **2b**. Thus, no reaction was observed at ambient temperature, but refluxing the reagents in methanol in the presence of catalytic amounts of trifluoroacetic acid led to immediate dehydration of compounds **2a**,**2b** to afford 1,2-azoles **5a** and **5b**.

The cyclic 1,2-azoline (Δ^2-isoxazoline and Δ^2-pyrazoline) structure **C** of compounds **4a-4f**, rather than pyrimidine **A** and **D** or linear **B**, follows from the spectral data: the presence of the typical *AB* pattern in ^{1}H NMR spectra (Table 2) and a signal of sp^3-hybrid C^5 atom in ^{13}C NMR spectra (Table 3). The position of the latter allows a choice of Δ^2-isoxazoline derivatives **4a-4c**,

δ_C 92 ppm (N-C-O environment), and Δ^2-pyrazolines **4d-4f**, δ_C 74 ppm (N-C-N environment). We observed previously a similar upfield shift ($\Delta\delta_C \sim 20$ ppm) for the linear analogues of hemiacetal and hemi-aminal fragments [8]. The signals in ^{1}H and ^{13}C NMR spectra of the previously studied series of 3,5-dimethyl-5-(*N*-phenylthioureido)-Δ^2-isoxazolines and -1-acetyl-Δ^2-pyra-zolines [1] agree well with the proposed structure of compounds **4a-4f**.

Additional evidence for the 1,2-azoline structure **C** of compounds **4a** and **4d** was provided by the possibility of their preparation through independent synthesis: reaction of phenyl isocyanate with 5-amino-3,5-dimethyl-Δ^2-isoxazoline **3a** and -1-acetyl-Δ^2-pyrazoline **3b**, which we described previously [1] (see Experimental).

Short refluxing of compounds **4a-4f** in methanol in the presence of catalytic amounts of sulfuric acid was found to give quantitative yields of 3,5-dimethylisoxazole **5a** and 1-acetyl-3,5-dimethylpyrazole **5b**. A comparison of physico-chemical and spectral data for these compounds (see Experimental) with literature analogues [9,10] confirms those structures.

Thus, the data considered, on the one hand, extends our insight into the mechanism of the pyrimidine – 1,2-azole recyclization [1-4,11] taking into account the intermediate formation of 5-uredo-Δ^2-isoxazolines and 5-uredo-1-acetyl-Δ^2-pyrazolines, and on the other hand, demonstrates the possibility of reverse transformation in the reaction of isocyanates with 3,5-disubstituted 5-amino-1,2-azolines.

Experimental Section

General Procedures. ^{1}H and ^{13}C NMR spectra were recorded on Bruker AC 200 spectrometer operating at 200 and 50.33 MHz, respectively. The purity of prepared compounds was controlled by TLC on Silufol UV 254 plates with 1:1 benzene-acetone eluent. All compounds gave satisfactory elemental analyses for C, H and N. Compounds **1a-1c**, **2a**,**2b**, **3a**,**3b**,**5a**, and **5b** were obtained by known procedures. Properties of the compounds obtained are in agreement with literature data [1,2,6,7].

5-(3-Arylureido)-3,5-dimethyl-Δ^2-isoxazolines 4a-4c and **5-(3-arylureido)-3,5-dimethyl-1-acetyl-Δ^2-pyrazolines 4d-4f.** *Method A*. A solution of 20 mmol of hydroxylamine base or acetylhydrazine and 20 mmol of sodium hydroxide in 30 ml of methanol and 10 ml of water was added with stirring to a solution of 10 mmol of compound **1a-1c** in 30 ml of methanol. The mixture was kept at 25 ^{o}C for 3 days. After neutralizing it with the dilute hydrochloric acid and removing the solvent under reduced pressure, 100 ml of water was added to the residue. The precipitate that formed was filtered off and recrystallized from an ethanol-water mixture, 1:1. *Method B*. A solution of 5 mmol of compound **3a** or **3b** and 5 mmol of phenyl isocyanate in 50 ml of chloroform was kept at 25 ^{o}C for 10 h. After the solvent was removed under reduced pressure, the residue was washed with ether and recrystallized from an ethanol-water mixture, 1:1.

3,5-Dimethylisoxazole 5a and **1-acetyl-3,5-dimethylpyrazole 5b**. A mixture of 5 mmol of compound **4a-4f**, 50 ml of methanol, and several drops of sulfuric acid was heated under reflux for 3 h. After the solvent was removed in a vacuum, 75 ml of ether and 25 ml of hexane was added to the residue. The crystalline matter was filtered off, and the filtrate was concentrated under reduced pressure to give compounds **5a,5b** in yields of 90 and 95%, respectively. ^{13}C NMR spectrum of compound **5a** ($CDCl_3$, δ_C, ppm): 10.8 (CH_3),11.6 (CH_3), 101.9 (C^4), 159.4 (C^3), 168.6 (C^5). ^{13}C NMR spectrum of compound **5b** ($CDCl_3$, δ_C, ppm): 13.2 (CH_3), 14.0 (CH_3), 22.9 (CH_3), 110.7 (C^4), 143.5 (C^5), 151.5 (C^3), 170.9 (C=O).

Table 1. Melting points, yields and elemental analysis data for Δ^2-isoxazolines and Δ^2-pyrazolines 4a-4f

Compd	Mp ^oC	Found, % / Calculated, %			Formula	Yield, %
		C	**H**	**N**		(*Method*)
4a	108-111	61.83 / 61.79	6.81 / 6.84	17.97 / 18.01	$C_{12}H_{15}N_3O_2$	50 (*A*); 70 (*B*)
4b	173-176	63.08 / 63.14	6.89 / 6.93	17.03 / 16.99	$C_{13}H_{17}N_3O_2$	45 (*A*)
4c	182-185	59.27 / 59.30	6.48 / 6.51	16.02 / 15.96	$C_{13}H_{17}N_3O_3$	60 (*A*)
4d	135-137	61.28 / 61.30	6.59 / 6.61	20.45 / 20.42	$C_{14}H_{18}N_4O_2$	45 (*A*); 75 (*B*)
4e	215-218	62.51 / 62.48	7.04 / 6.99	19.39 / 19.43	$C_{15}H_{20}N_4O_2$	50 (*A*)
4f	195-197	59.22 / 59.19	6.58 / 6.62	18.46 / 18.41	$C_{15}H_{20}N_4O_3$	55 (*A*)

Table 2. ^{1}H NMR spectra of Δ^2-isoxazolines and Δ^2-pyrazolines 4a-4f in DMSO-d_6, δ, ppm (J, Hz)

Compd	CH_3C^3, s, 3H	CH_3C^5, s, 3H	R, s, 3H	H^4, *AB* pattern, 2H	$H_{arom.}$	2NH, br.s, 2H
4a	1.89	1.58	–	2.81; 3.38 (18)	6.95–7.38 (5H)	7.42; 8.44
4b	1.89	1.59	2.23	2.80; 3.39 (18)	7.03–7.25 (4H)	7.06; 8.30
4c	1.90	1.58	3.71	2.81; 3.39 (18)	6.72–7.28 (4H)	6.71; 8.22
4d[a]	1.91	1.68	–	2.77; 3.45 (19)	6.96–7.38 (5H)	7.46; 8.67
4e[a]	1.94	1.67	2.21	2.78; 3.45 (19)	7.02–7.23 (4H)	6.87; 8.51
4f[a]	1.95	1.68	3.68	2.75; 3.43 (18)	6.73–7.35 (4H)	6.73; 8.49

[a] Methyl protons of *N*-acetyl group display signals at 2.10 ppm (s, 3H).

Table 3. ^{13}C NMR spectra of Δ^2-isoxazolines and Δ^2-pyrazolines 4a-4f in DMSO-d_6, δ_C, ppm

Compd	$\underline{C}H_3C^3$	$\underline{C}H_3C^5$	R	C^3	C^4	C^5	C=O	C_{arom}
4a	13.1	26.5	–	155.6	47.9	92.4	153.6	117.9–139.2
4b	13.1	26.5	20.4	155.5	47.9	92.5	153.6	118.0–137.4
4c	13.1	26.6	55.2	155.5	47.9	92.5	153.8	114.0–154.3
4d[a]	15.8	26.2	–	154.4	50.0	74.6	153.9	117.7–140.0
4e[a]	15.7	26.2	20.3	154.3	50.0	74.6	153.9	117.7–137.6
4f[a]	15.8	26.3	55.2	154.4	50.1	74.7	153.1	114.0–154.2

[a] Carbon atom of *N*-acetyl group display at 22.5 (CH_3) and 167.3 ppm (C=O).

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