NOVEL SYNTHESIS OF 2-THIOCYTOSINE DERIVATIVES VIA PYRIMIDINE-TO-PYRIMIDINE RING TRANSFORMATION

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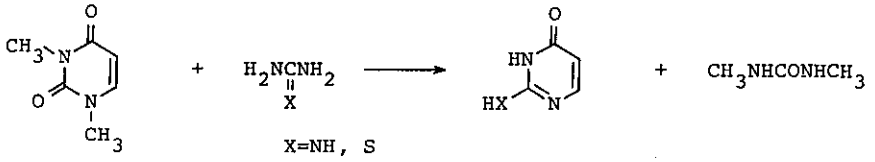
Abstract —— The reaction of 1,3-disubstituted 5-cyanouracils (1) with thioureas (2) and sodium hydroxide causes novel pyrimidine-to-pyrimidine ring transformation to give 2-thiocytosines (3) and 6-amino-5-formyluracils (4), respectively.

Our previous works have demonstrated[1] that the reaction of uracil derivatives with various 1,3-ambident nucleophiles causes an intermolecular ring-transfragment reaction[2] involving the apparent displacement of an appropriate fragment of the uracil ring by the nucleophiles. For example, when 1,3-dimethyluracil is allowed to react with guanidine and thiourea, the corresponding 2-amino- and 2-mercaptopyrimidines are obtained, respectively. These ring transformations resulted in the displacement of the N(1)-C(2)-N(3) fragment of the uracil by the N-C-N fragment of the nucleophiles (Scheme 1).[1a] During our investigation on the reaction of 5-cyanouracils[3] with thioureas, we have found novel pyrimidine-to-pyrimidine ring transformation leading to 2-thiocytosines (3) and 6-amino-5-formyluracils (4).

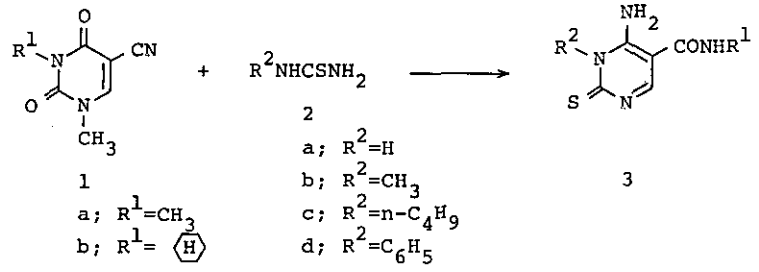


Scheme 1

Treatment of 5-cyano-1,3-dimethyluracil (**1a**) with 3 molar equivalents each of thiourea (**2a**) and sodium hydroxide in ethanol under reflux for 10 min led to the

formation of 5-N-methylcarbamoyl-2-thiocytosine (**3a**)[4,5] in 75% yield along with a trace amount of 6-amino-5-formyl-1,3-dimethyluracil (**4a**).[6] The structure of **3a** was supported by the spectral and microanalytical data,[7] and confirmed by the direct comparison with an authentic sample prepared by the reaction of 5-ethoxycarbonyl-2-thiocytosine[8] with methylamine. Analogous treatment of **1a** with methyl-, butyl-, and phenylthioureas (**2b-d**) gave the corresponding 3-substituted 2-thiocytosines (**3b-d**), respectively, in good yield.

In order to determine a source of the 5-carbamoyl group, the reaction of 5-cyano-3-cyclohexyl-1-methyluracil (**1b**), possessing different substituent at N(1)- and N(3)-positions, with thioureas (**2a** and **2b**) was carried out. Both reactions afforded the corresponding 5-(N-cyclohexylcarbamoyl)-2-thiocytosines (**3e** and **3f**), respectively. This result clearly shows that the N-substituent of 5-carbamoyl group of **3** originates from N(3)-substituent of the parent uracils (**1**). The UV spectra of the 3-substituted 2-thiocytosines (**3b-d** and **f**) (see Table) are superimposable on that of 5-ethoxycarbonyl-3-methyl-2-thiocytosine [221 (ε 10500), 292 (ε 12300), and 351 nm (ε 21200)].[8]



1
a; R^1=CH_3
b; R^1= ⟨H⟩

2
a; R^2=H
b; R^2=CH_3
c; R^2=n-C_4H_9
d; R^2=C_6H_5

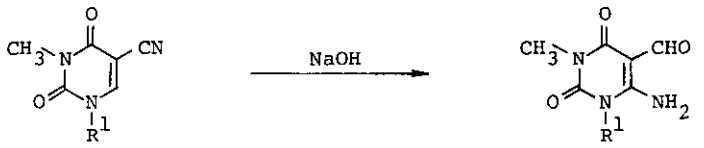
3

Scheme 2

Table 5-Carbamoyl-2-thiocytosine derivatives (3)

No.	R^1	R^2	Mp °C	Yield %	UV spectra (λ_{max}^{EtOH}, nm, ε)
3a	CH_3	H	276.5-277.5	75	241 (14700), 299 (23600)
3b	CH_3	CH_3	264.5-265	88	224 (11200), 291 (13000), 355 (17500)
3c	CH_3	n-C_4H_9	224-225	41	226 (11100), 293 (13100), 358 (17100)
3d	CH_3	C_6H_5	227-228	75	225 (15900), 293 (13500), 363 (14800)
3e	⟨H⟩	H	>300	81	241 (15800), 299 (26000)
3f	⟨H⟩	CH_3	256-258	59	227 (9600), 291 (13400), 355 (18300)

In the above reaction, the formation of a trace amount of the 6-amino-5-formyluracil (**4a**) was observed and its molecule does not contain the fragment arising from thioureas. This fact prompts us to examine the reaction in the absence of thioureas. The reaction of **1a** with sodium hydroxide in ethanol under reflux for 7 h gave in accord with expectations the 6-amino-5-formyluracil (**4a**) as the sole product in 58% yield. Analogous reaction of 5-cyano-3-methyl-1-phenyluracil (**1c**) with sodium hydroxide gave the corresponding 6-amino-5-formyluracil (**4b**)[6] in 82% yield even upon heating for a short time (10 min). The introduction of phenyl group at the 1-position facilitates cleavage of the 1,6-bond in the uracil ring.[9] Therefore, this result suggests that the 1,6-bond cleavage is a key step for this ring transformation.

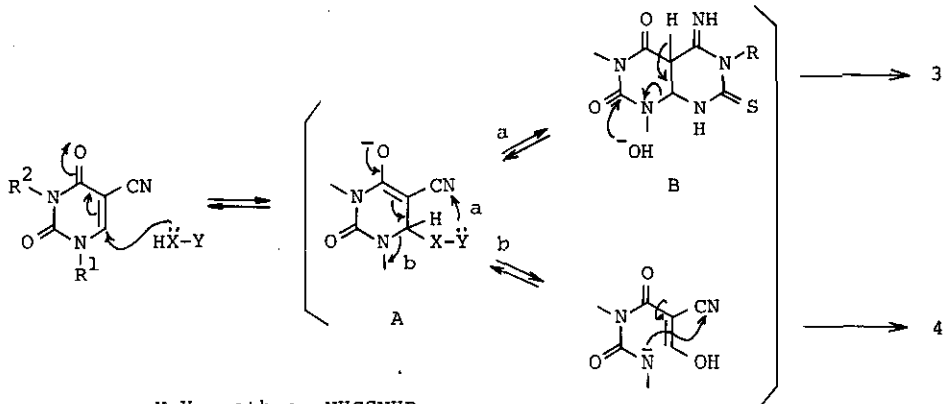


1
a; $R^1=CH_3$
c; $R^1=C_6H_5$

4
a; $R^1=CH_3$
b; $R^1=C_6H_5$

Scheme 3

Plausible mechanisms for the present ring transformations are outlined in Scheme 4. An initial attack of the nucleophile on the 6-position affords an adduct **A**. In the case of the thiourea, cyclization between the terminal amino group of the thiourea and the 5-cyano group preferentially occurs and produces an intermediate **B**, which subsequently undergoes hydrolysis, decarboxylation, and deamina-



X-Y= path a; NHCSNHR
path b; OH

Scheme 4

tion leading to 3 (path a). The formation of 4 can be explained in terms of an intramolecular rearrangement involving the 1,6-bond cleavage of **A** and subsequent recyclization of an open-chain intermediate **C** (path b). The latter ring transformation is mechanistically similar to the ring transformation reported by Su and Watanabe.[10]

REFERENCES AND NOTES

1 a) K. Hirota, K.A. Watanabe, and J.J. Fox, J. Org. Chem., 1978, **43**, 1193; b) K. Hirota, Y. Kitade, S. Senda, M.J. Halat, K.A. Watanabe, and J.J. Fox, J. Am. Chem. Soc., 1979, **101**, 4423; c) idem, J. Org. Chem., 1981, **46**, 846; d) K. Hirota, Y. Kitade, and S. Senda, Tetrahedron Lett., 1981, **22**, 2409; e) idem, J. Chem. Soc., Perkin 1, in press.

2 This terminolgy represents most adequately the nature of our ring transformation in order to distinguish it from intramolecular rearrangements, such as the Dimroth rearrangement or photochemical transposition reaction; see the reference 1c.

3 Starting 5-cyanouracils were prepared according to the previously reported procedure; S. Senda, K. Hirota, and J. Notani, Chem. Pharm. Bull., 1972, **20**, 1380.

4 All new compounds gave satisfactory microanalytical results and spectral data consistent with their proposed structures.

5 For convenient drawings, 3-unsubstituted 2-thiocytosines (**3a** and **3e**) were represented as their 3H form at the N(3)-position, respectively.

6 Compounds **4a**[6a] and **4b** were alternatively prepared by the Vilsmeier reaction of the corresponding 6-aminouracils; 6a) H. Bredereck, G. Simchen, R. Wahl, and F. Effenberger, Chem. Ber., 1968, **101**, 512.

7 **3a**: ^{1}H-NMR (60 MHz, in DMSO-d_6) 2.68 (3H, d, CH_3, collapsing with D_2O to singlet), 7.98 (1H, s, C_6-H), 8.45 (2H, br, NH_2), and 12.41 (1H, br, NH).

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