Palladium-Catalyzed Polyhetero-Claisen Rearrangement of 2-(Allylthio)pyrimidin-4(3*H*)-ones

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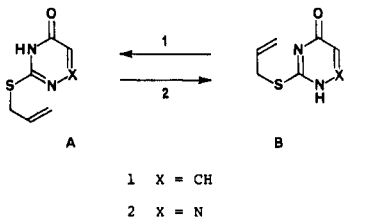
The regioselective S → N allylic transposition of 2-(allylthio)pyrimidin-4(3*H*)-ones (**3**) has been performed by catalysis of Pd(II) salts. Generally the rearrangement gives the N-1 alkylation product predominantly over the N-3 alkylation product. Substituents at the 6-position of **3** reverse the selectivity. Both N-1 and N-3 rearrangement products were transformed to thiazolopyrimidones.

Despite the synthetic utility of S → N allylic rearrangement (a general structural transformation, N=CS-CC=C → S=CNCC=C), the lack of structure–reactivity correlations limits this rearrangement for general use. For example, 2-(allylthio)benzimidazoles,[1] 2-(allylthio)benzthiazoles,[2] and 2-(allylthio)imidazolines[3] undergo thermal S → N allylic rearrangement, whereas, 5-(allylthio)pyrimidines[4] and 8-(allylthio)caffeines[1] do not. Previously we have reported that Pd(II) salts effectively catalyze the thermally prohibited or very slow S → N allylic transposition of (*S*)-(allylthio)imidates.[5] Furthermore, we have demonstrated that this reaction can be applied to the reaction giving secondary thioamides which have been thought to be a catalyst poison owing to their strong coordination to Pd(II) salts.[6] During our study on the synthesis of new anticancer agents, we required a general regioselective N-alkylation method (N-1 or N-3) of uracil, the derivatives of which are of interest due to their biological activities (e.g., 5-fluorouracil,[7] an anticancer agent). In this paper, we have demonstrated that palladium salts catalyze the regioselective S → N allylic rearrangement of 2-(allylthio)pyrimidin-4(3*H*)-ones. We also refer to some mechanistic aspects of this reaction, which explain the present unique regioselectivity. The high yield cyclization of the rearranged products to thiazolopyrimidones is also presented.

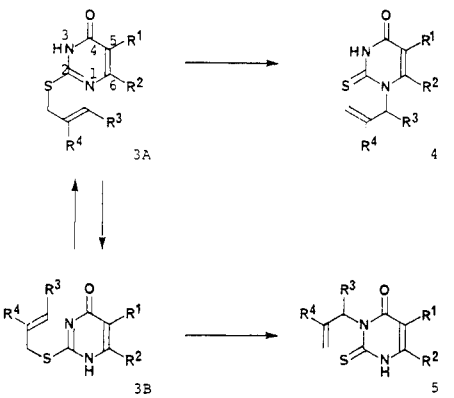
Results and Discussion

In a previous paper,[6] we have reported that Pd(II) salts catalyze an allylic rearrangement of 3-(allylthio)-1,2,4-triazin-5(2*H*)-ones (**2**) to selectively provide the N-4 alkylated products, reflecting the predominance of tautomer **2B** over 2A (Scheme I). Pyrimidin-4(3*H*)-ones (**1**), on the other hand, as indicated from spectroscopic studies,[8] exist mostly in tautomeric form **1A** at equilibrium and are expected to provide the N-1 alkylation product under our palladium-catalyzed reaction conditions. This proved to be the case and this palladium-catalyzed rearrangement complements the direct alkylation of **1**, which is known to provide the N-3 alkylation product albeit in moderate or low yields (vide infra, **11** → **10a**, Scheme IV).[9]

Scheme I



Scheme II



	R^1	R^2	R^3	R^4
a	H	H	H	H
b	CH_3	H	H	H
c	H	CH_3	H	H
d	H	$i\text{-}C_3H_7$	H	H
e	H	H	CH_3	H
f	H	CH_3	CH_3	H
g	H	H	H	CH_3

Pd(II)-Catalyzed S → N Allylic Rearrangement. Initially, thermal rearrangement of **3** was examined, and up to 150 °C only the starting material was recovered (e.g., **3c**, 150 °C, 6 h). In marked contrast to this result, the

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(8) Brown, D. J.; Hoerger, E.; Mason, S. F. *J. Chem. Soc.* **1955**, 211.
(9) Alkylation of 2-(methylthio)pyrimidin-4(3*H*)-ones has been reported to give the N-3 product in low yield, which is contaminated with the N-1 side product. (a) Gacek, M.; Undheim, K. *Acta Chem. Scand., Ser. B* **1979**, *B 33*, 515. (b) Minnemeyer, H. J.; Clarke, P. B.; Tieckelmann, H. *J. Org. Chem.* **1966**, *31*, 406.

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Table I. Pd(II)-Catalyzed S → N Allylic Rearrangement of 2-(Allylthio)pyrimidin-4(3*H*)-ones

entry	pyrimidone 3	$PdCl_2(PhCN)_2$, mole %	reactn conditn	convertn, %	yield,[a] %	ratio of 4:5
1	**3a**	2	THF, reflux, 4 h	100	96	93:7
2	**3b**	2	THF, reflux, 4 h	100	93	93:7
3	**3c**	4	THF, rt,[c] 13 h	87	70	80:20
4	**3c**	10	THF, reflux, 8 h	100	82	8:92
5	**3d**	4	THF, reflux, 8 h	67	97	9:91
6	**3e**	2	THF, reflux, 2 h	97	93	100:0
7	**3f**	5	THF, reflux, 7 h	30	63	0:100
8	**3g**	10	dioxane, reflux, 10 h	100	*b*	

[a] Isolated yield based on conversion. [b] Intractable mixture of products. [c] rt = room temperature.

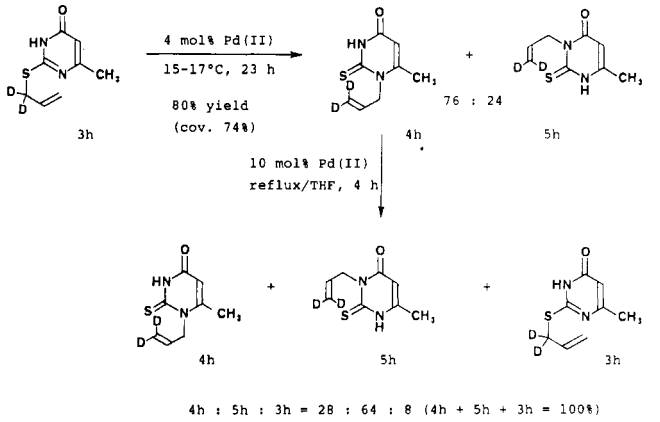
presence of a catalytic amount of $PdCl_2(PhCN)_2$ provided the rearranged products **4** and/or **5** in high yields at 25–65 °C (Scheme II). These results, together with the reaction conditions, are summarized in Table I, which reveals that the selectivity between **4** and **5** is very high but dependent both on the reaction conditions and the substitution pattern on C-6 (R^2 substituent) and allylic terminus (R^3).

In good accordance with the expectation based on the preference of **3A** over **3B** at equilibrium, when $R^2 = R^3 = H$ (**3a**, **3b**), N-1 alkylation took place selectively, providing **4a** and **4b**, respectively, irrespective of the substituent R^1. When $R^2 = CH_3$ and $R^3 = H$ (entry 3 in Table I), the selectivity for **4c** over **5c** is lower than those of the above two cases. On the other hand, in the case of **3e** (entry 6 in Table I), the reaction produced the N-1 alkylated product exclusively and no traces of N-3 product were detected. This high N-1 alkylation may be due to a pseudo-A(1,3) interaction[10] between the C-4 carbonyl oxygen and the terminal methyl group assuming a chair-like transition state for the N-3 alkylation reaction. The completely reversed selectivity observed in entry 7 also may be explained on steric grounds. Repulsion between $R^2 = CH_3$ and $R^3 = CH_3$ prohibits the rearrangement to the N-1 nitrogen atom and forces the rearrangement to take place to the N-3 nitrogen atom.

That the product distribution was kinetically controlled (except entry 4 and probably entry 5, vide infra) is apparent from the following observations: (1) No isomerization of **4a** to **5a** or vice versa was observed under the THF reflux rearrangement conditions. (2) Only methallyl type products and no traces of crotyl type products were obtained (entries 6 and 7 in Table I). This complete allylic inversion indicates that the reaction proceeds in an intramolecular fashion. We could not obtain any rearrangement products in the case of **3g** (entry 8 in Table I). These results are in good accordance with those observed for the Pd(II)-catalyzed S → N allylic rearrangement of thioimidates reported previously from these laboratories and support the mechanism proposed therein.[5a,11]

Interestingly, when $R^2 = CH_3$ and $R^3 = R^4 = H$ (entries 3 and 4 in Table I), the reaction proceeds with exceptional ease and product distributions are highly dependent on the reaction conditions. At room temperature **4c** was obtained as a main product, while at the THF refluxing temperature **5c** was produced as a main product. In order to elucidate the details of this unique behavior, we found that in the presence of Pd(II) catalyst, **4c** changed to **5c** at 65 °C, but not at 25 °C, whereas **5c** remained unchanged under THF reflux conditions. Apparently the isomerization of **4c** to **5c** is due to Pd(II)-catalysis, since thermal treatment of **4c** (THF, 65 °C, 4 h) provided no trace of **5c**.

Scheme III



These results indicated that the ratio in entry 3 reflects the selectivity of rearrangement of **3c** done under kinetic conditions and the ratio in entry 4 under thermodynamic conditions. Although we could not follow the details of the rearrangement of **3d**, mainly owing to its slowness at room temperature, the results in entry 5 may be explained as a result of the thermodynamically controlled experiments. Taking into consideration that **4a** does not isomerize to **5a** under the above thermodynamic conditions (vide supra), the isomerization of **4c** to **5c** may stem from destabilization of **4c** caused by a steric repulsion between the allyl (N-1) and methyl (C-6) groups.

To get closer insight into the **4c** → **5c** rearrangement, Pd(II)-catalyzed rearrangement was performed with the sample **3h**, specifically dideuterium labeled at the allylic position (Scheme III). Under the condition similar to those in entry 3, **3h** rearranged to provide a mixture of **4h** and **5h** in a ratio of 76:24. Specific dideuterium labeling at the olefinic terminal protons were determined on the basis of the ^1H NMR spectra of the isolated **4h** and **5h**. When sample **4h** was then subjected to the conditions similar to those of entry 4, a mixture of **4h** (28%) and **5h** (64%) including, quite interestingly, **3h** (8%) was obtained. Here again, no scrambling of the deuteriums occurred and specific dideuterium labels were observed at the olefinic terminal positions both in **4h** and **5h** and at the allylic position in **3h**. The formation of **5h** and **3h** starting from **4h** apparently indicates that the rearrangement of **4h** to **5h** proceeds stepwise through an equilibrium between **4h** and **3h**. The regiospecificity of deuterium labeling in **3h**, **4h**, and **5h** excludes the possibilities of mechanisms involving intermolecular allylic transposition or mechanism involving direct allylic rearrangement from the N-1 to the N-3 position via the iminothiol form of **4**.

Structure Determination of the Rearrangement Products 4 and 5. The thiones **4** and **5** in entries 1–7 in Table I were purified by means of column chromatography over silica gel. The ratio of **4** to **5** was determined on the basis of their isolated yields. The mass spectra of both **4** and **5** have the same parent peak as the starting pyrimi-

(10) (a) Johnson, F. *Chem. Rev.* **1968**, *68*, 375. (b) Hart, D. J. *J. Am. Chem. Soc.* **1980**, *102*, 397; also his extensive current works. (c) Wilson, S. R.; Misra, R. N. *J. Org. Chem.* **1980**, *45*, 5079. (d) Overman, L. E.; Yokomitsu, T. *Ibid.* **1980**, *45*, 5229.

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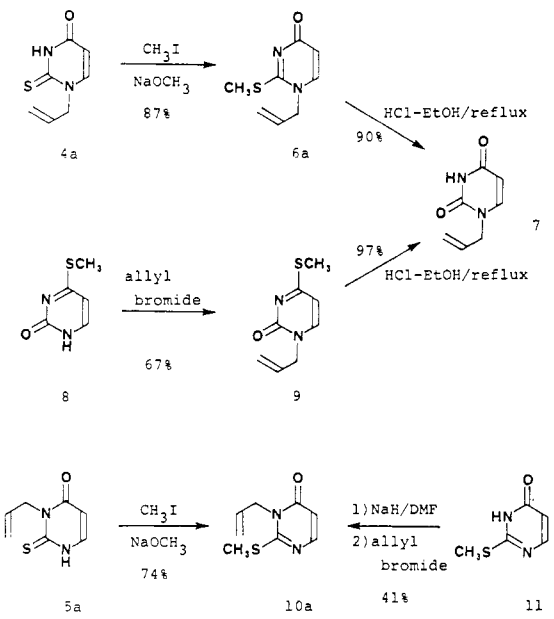
Table II. Ultraviolet Spectra of 1-Allyl-2-(methylthio)pyrimidin-4(1*H*)-ones (6) and 2-(Methylthio)-3-allylpyrimidin-4(3*H*)-ones (10)

entry	pyrimidinedione	pyrimidone (% isolated yield)[a]	UV spectra of 6 and 10 λ_{max}^{EtOH}, nm (ϵ)
1	**4a**	**6a** (87)	236 (27 300)
2	**5a**	**10a** (74)	295 (10 200), 228 (6700), 207 (11 700)
3	**4b**	**6b** (91)	236 (27 900)
4	**5b**	**10b** (58)	293 (8800), 225 (4200), 206 (8100)
5	**4c**	**6c** (75)	235 (28 800)
6	**5c**	**10c** (70)	291 (11 100), 227 (6700), 205 (13 400)
7	**5d**	**10d** (92)	291 (11 300), 227 (7200), 206 (16 100)
8	**4e**	**6e** (91)	236 (27 800)
9	**5f**	**10f** (50)	291 (12 700), 227 (9500), 205 (19 400)

[a] Both **6** and **10** were prepared from **4** and **5**, respectively, according to a standard method (cf. Scheme IV).

Scheme IV



dones **3**. The allylic methylene protons of **4** and **5** absorbed in the NMR in the region of δ 4.7–5.1 (except **4e** and **5f**). The spectra of the crotyl type products (**4e** and **5f**) showed no allylic methylene protons; only allylic methine protons absorptions were observed. These results clearly indicate that **4** and **5** are the rearranged products. However none of the derivatives **4** or **5** showed any characteristic IR, ^{1}H NMR, or mass spectral absorptions. Accordingly, the structure of **4a** and **5a** was determined on the basis of the following chemical conversions (Scheme IV).[12]

S-Methylation of **4a** followed by acid hydrolysis afforded 1-allyluracil (**7**) which showed identical spectral and physical properties (^{1}H NMR, IR, mass, melting point) with those of an authentic sample.[13] Also **7** was provided by allylation of **8**[9a] and subsequent acid hydrolysis. Treatment of **5a** with methyl iodide furnished **10a** whose structure was confirmed by comparison with an authentic sample prepared by the reaction of **11** with allyl bromide.[9a] The structures of other derivatives of **4** and **5** may be determined by a similar laborius sequence.

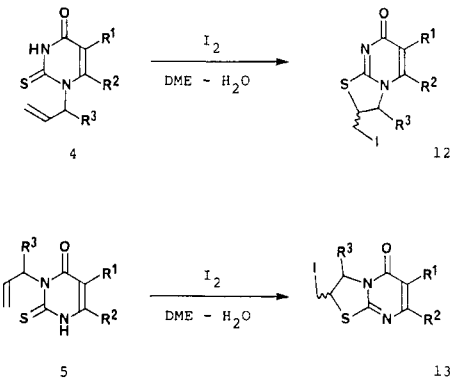
Another basis for distinguishing **4** from **5** is the comparisons of the ultraviolet spectra of S-methylated products, e.g., **6** and **10**, respectively. The absorption maxima of quinone (**6**) are known to be more intense and to lie at shorter wavelengths than those of dienone **10**.[8] As shown in Table II, both series of quinone type products **6a–c** and **6e** and of dienone type products **10a–d** and **10f** showed their characteristic absorptions.

Table III. Iodo Thiol Imino Lactonization of Allyl-2-thiouracils 4 and 5[a]

entry	pyrimidinedione	thiazolopyrimidone	yield,[b] %	UV spectra of 12 and 13 λ_{max}^{EtOH}, nm (ϵ)
1	**4a**	**12a**	80	232 (29 300)
2	**4b**	**12b**	72	232 (27 900)
3	**4e**	**12**[c]	93	232 (28 900)
4	**5c**	**13c**	98	290 (7700), 233 (7700) 207 (12 100)

[a] Reaction Conditions: I_2 (1.1 equiv.) in DME–H_2O at room temperature (Scheme V). [b] Yields refer to the isolated ones. [c] A mixture (ca. 3:2) of diastereomers was obtained.

Scheme V



Halo Thiol Imino Lactonization of 4 and 5. In order to further demonstrate the utility of the present reaction, we tried halo thiol imino lactonization of allyluracils **4** and **5**. Bromo and iodo thiol imino lactonization of 3-allyl-2-thiouracils already has been reported to give 5*H*-thiazolo[3,2-*a*]pyrimidin-5-ones.[14] According to the similar but somewhat modified procedure (1.1 equiv of I_2 in DME–H_2O at room temperature),[15] the cyclization of **4** and **5** was found to proceed smoothly to provide 2,3-dihydro-7*H*-thiazolo[3,2-*a*]pyrimidin-7-ones (**12**) and 2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidin-5-ones (**13**), respectively, in high yields (Scheme V, Table III). The structure of **12** and **13** was deduced from analytical and spectral data. The elucidation of the structure of **12** and **13** was based on their UV spectra (Table III). The shapes and positions of the absorptions of **12** and **13** were similar to those of **6** and **10**, respectively.

(12) Compound **4a** is known. Dinan, F. J.; Minnemeyer, H. J.; Tieckelmann, H. *J. Org. Chem.* **1963**, *28*, 1015.
(13) Tanabe, T.; Yamauchi, K.; Kinoshita, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 259.
(14) (a) Giambrone, S. *Boll. Sci. Fac. Chim. Ind. Bologna* **1953**, *11*, 86; *Chem. Abstr.* **1955**, *49*, 4662e. (b) Ajello, T.; Miraglia, A. *Gazz. Chim. Ital.* **1948**, *78*, 921; *Chem. Abstr.* **1949**, *43*, 6985b.
(15) Tamaru, Y.; Mizutani, M.; Furukawa, Y.; Kawamura, S.; Yoshida, Z.; Yanagi, K.; Minobe, M. *J. Am. Chem. Soc.* **1984**, *106*, 1079.

Experimental Section

Melting points were determined in capillary tubes with a Mettler FP 61 instrument and were uncorrected. Short-path (bulb-to-bulb) distillations were carried out in a Kugelrohr apparatus. Microanalyses were obtained with a Perkin-Elmer 240 or 240B instrument. Measurement of infrared spectra was made on a Hitachi 260-10 spectrometer. Proton magnetic resonances (^{1}H NMR) spectra were measured at 60 MHz on a Hitachi R-24B NMR spectrometer taking tetramethylsilane as an internal standard. Mass spectra were run on a Shimadzu LKB-9000B instrument. Ultraviolet spectra were obtained with a Hitachi 220 spectrometer. Infrared and mass spectra and analytical data for individual compounds **3–7**, **9**, **10**, **12**, and **13** are recorded in supplementary material (see the paragraph at the end of the paper).

Solvents and Reagents. Tetrahydrofuran and dioxane were dried and distilled from benzophenone and sodium under nitrogen atmosphere immediately prior to use. Methyl alcohol and dimethylformamide were stored over molecular sieves, 3A. Allyl bromide, *trans*-crotyl bromide, and methallyl chloride were purchased from Wako Pure Chemical Industries, Ltd.

2-(Allylthio)pyrimidin-4(3*H*)-ones (3a–g). General Procedure. To a stirred solution of 2-thiouracil [$R^1 = R^2 = H$ (**3a**, **3e**, **3g**); $R^1 = CH_3$, $R^2 = H$ (**3b**); $R^1 = H$, $R^2 = CH_3$ (**3c**, **3f**); $R^1 = H$, $R^2 = i$-C_3H_7 (**3d**); 10 mmol] and sodium methoxide (11 mmol) in MeOH (30 mL) was added allyl halide [allyl bromide (**3a–d**), *trans*-crotyl bromide (**3e**, **3f**), methallyl chloride (**3g**); 13 mmol] at room temperature. The reaction mixture was stirred overnight at the same temperature except **3g**. For the preparation of **3g** the reaction was conducted at 70 °C for 6 h. The solvent was removed under reduced pressure. In the case of **3b–f**, the residue was partitioned between $CHCl_3$ and H_2O, and the organic extract was dried over $MgSO_4$ and concentrated to give crude **3**, which was recrystallized to yield pure compound **3**. In the case of **3a** and **3g**, after the addition of H_2O to the residue, the precipitate was collected by filtration and washed with H_2O. The crude product **3** was recrystallized from *n*-hexane–acetone to afford pure compound **3**.

3a: mp 136.0 °C (EtOH); yield 29%; ^{1}H NMR (Me_2SO-d_6) δ 3.80 (d, J = 6.6 Hz, 2 H), 5.02–6.15 (m, 3 H), 6.15 (d, J = 7.2 Hz, 1 H), 7.91 (d, J = 7.2 Hz, 1 H).

3b: mp 165.5 °C (EtOH); yield 57%; ^{1}H NMR ($CDCl_3$–Me_2SO-d_6) δ 1.99 (s, 3 H), 3.78 (d, J = 6.6 Hz, 2 H), 4.97–5.42 (m, 2 H), 5.60–6.29 (m, 1 H), 7.68 (s, 1 H).

3c: mp 134.2 °C (*n*-hexane–acetone–EtOH); yield 79%; ^{1}H NMR ($CDCl_3$) δ 2.21 (s, 3 H), 3.78 (d, J = 6.6 Hz, 2 H), 4.92–6.07 (m, 3 H), 5.95 (s, 1 H).

3d: mp 100.7 °C (*n*-hexane–acetone); yield 81%; ^{1}H NMR ($CDCl_3$) δ 1.24 (d, J = 6.9 Hz, 6 H), 2.45–3.13 (m, 1 H), 3.89 (d, J = 6.6 Hz, 2 H), 5.04–5.48 (m, 2 H), 5.67–6.22 (m, 1 H), 6.08 (s, 1 H).

3e: mp 139.8 °C (*n*-hexane–EtOH); yield 55%; ^{1}H NMR ($CDCl_3$) δ 1.65 (d, J = 4.8 Hz, 3 H), 3.76 (d, J = 5.4 Hz, 2 H), 5.42–5.78 (m, 2 H), 6.15 (d, J = 6.6 Hz, 1 H), 7.79 (d, J = 6.6 Hz, 1 H).

3f: mp 132.8 °C (*n*-hexane–EtOH); yield 75%; ^{1}H NMR ($CDCl_3$) δ 1.64 (d, J = 4.8 Hz, 3 H), 2.20 (s, 3 H), 3.74 (d, J = 5.4 Hz, 2 H), 5.39–5.76 (m, 2 H), 5.97 (s, 1 H).

3g: mp 101.1 °C (*n*-hexane–acetone); yield 47%; ^{1}H NMR (Me_2SO-d_6) δ 1.80 (s, 3 H), 3.90 (s, 2 H), 4.93 (s, 1 H), 5.08 (s, 1 H), 6.16 (d, J = 6.6 Hz, 1 H), 7.92 (d, J = 6.6 Hz, 1 H).

2-[(Allyl-*1,1*-d_2)thio]-6-methylpyrimidin-4(3*H*)-one (3h). The dideuterium labeled compound **3h** was prepared by the reaction of 6-methyl-2-thiouracil with 2-propenyl-*1,1*-d_2 chloride which was obtained by the chlorination of 2-propen-1-ol-*1,1*-d_2[16] according to the method reported by Hooz and Gilani.[17] To the solution of propen-1-ol-*1,1*-d_2 (2.32 g, 38.6 mmol) and carbon tetrachloride (40 mL) was added tri-*n*-butylphosphine (8.50 g, 42 mmol) at 0 °C for 10 min. The chloride (1.46 g, 48% yield) was distilled at 40–50 °C through a 8-cm Vigreux column. A mixture of 6-methyl-2-thiouracil (1.03 g, 7.23 mmol), sodium methoxide (0.43 g, 7.95 mmol), and 2-propenyl-*1,1*-d_2 chloride (1.14 g, 14.5 mmol) in MeOH (30 mL) was heated at 40–50 °C for 9 h. Similar workup to that in the case of **3c** gave **3h** (0.95 g, 72%) which isotopic purity was determined by ^{1}H NMR to be greater than 97%: mp 134.6 °C (*n*-hexane–acetone); ^{1}H NMR ($CDCl_3$) δ 2.11 (s, 3 H), 5.00–5.45 (m, 2 H), 5.70–6.17 (m, 1 H), 6.03 (s, 1 H).

S → N Allylic Rearrangement. (A) Thermal Rearrangement. Thermal treatment of **3c** (neat, at 150 °C for 6 h) provided only the starting material. This complete recovery and the absence of **4a** and **5a** were thoroughly checked by ^{1}H NMR and TLC.

(B) Pd(II)-Catalyzed S → N Allylic Rearrangement. General Procedure. A THF or dioxane solution of **3** (1 mmol) and $PdCl_2(PhCN)_2$ (indicated amounts in Table I) was stirred under the conditions shown in Table I. After evaporation of the solvent, the residue was directly subjected to a column purification [silica gel, *n*-hexane–ethyl acetate gradient (**3a,b**), *n*-hexane–acetone gradient (**3c–g**)] to give the spectroscopically pure compounds **4** and **5** (**5** was eluded first). In entry 8 in Table I, no characterizable products were obtained. Analytically pure samples were obtained by recrystallization.

4a: mp 189.8 °C (*n*-hexane–acetone); ^{1}H NMR (Me_2SO-d_6) δ 4.73 (d, J = 5.4 Hz, 2 H), 4.88–5.30 (m, 2 H), 5.44–6.18 (m, 1 H), 5.86 (d, J = 7.8 Hz, 1 H), 7.63 (d, J = 7.8 Hz, 1 H).

5a: mp 119.2 °C (n-hexane - acetone); ^{1}H NMR ($CDCl_3$) δ 4.86 - 5.40 (m, 4 H), 5.56 - 6.20 (m, 1 H), 5.96 (d, J = 7.2 Hz, 1 H), 7.03 (dd, J = 6.0, 7.2 Hz, 1 H).

4b: mp 149.9 °C (*n*-hexane–acetone); ^{1}H NMR ($CDCl_3$) δ 1.93 (s, 3 H), 4.64–5.50 (m, 4 H), 5.52–6.22 (m, 1 H), 7.03 (s, 1 H).

5b: mp 155.5 °C (*n*-hexane–acetone); ^{1}H NMR ($CDCl_3$) δ 1.94 (s, 3 H), 4.85–5.40 (m, 4 H), 5.57–6.20 (m, 1 H), 6.95 (s, 1 H).

4c: mp 166.6 °C (*n*-hexane–acetone); ^{1}H NMR (acetone-d_6) δ 2.38 (s, 3 H), 4.91–5.38 (m, 4 H), 5.63–6.38 (m, 1 H), 5.79 (s, 1 H).

5c: mp 191.1 °C (*n*-hexane–acetone); ^{1}H NMR ($CDCl_3$–acetone-d_6) δ 2.19 (s, 3 H), 4.78–5.33 (m, 4 H), 5.52–6.15 (m, 1 H), 5.66 (s, 1 H).

5d: mp 158.6 °C (*n*-hexane–acetone); ^{1}H NMR ($CDCl_3$) δ 1.25 (d, J = 6.9 Hz, 6 H), 2.32–3.00 (m, 1 H), 4.87–5.43 (m, 4 H), 5.59–6.23 (m, 1 H), 5.81 (s, 1 H).

4e: mp 172.5 °C (*n*-hexane–EtOH); ^{1}H NMR ($CDCl_3$) δ 1.44 (d, J = 6.6 Hz, 3 H), 5.09–6.39 (m, 4 H), 5.96 (d, J = 7.5 Hz, 1 H), 7.17 (d, J = 7.5 Hz, 1 H).

5f: mp 157.4 °C (*n*-hexane–EtOH); ^{1}H NMR ($CDCl_3$) δ 1.72 (d, J = 6.6 Hz, 3 H), 2.18 (s, 3 H), 5.02–5.48 (m, 2 H), 5.75 (s, 1 H), 6.00–6.50 (m, 2 H).

Pd(II)-Catalyzed S → N Allylic Rearrangement of 3h. A THF (15 mL) solution of **3h** (553 mg, 3 mmol) and $PdCl_2(PhCN)_2$ (46 mg, 0.12 mmol) was stirred at 15–17 °C for 23 h. After evaporation of the solvent, the residue was directly subjected to a column chromatography (silica gel, *n*-hexane–acetone gradient) to provide **5h** (77 mg), **3h** (145 mg), and **4h** (250 mg). The isotopic purity of **4h** and **5h** was determined to be greater than 97% on the basis of ^{1}H NMR area intensities. The combined yield of **4h** and **5h** was 80% based on 74% conversion.

4h: mp 166.3 °C (*n*-hexane–acetone); ^{1}H NMR ($CDCl_3$) δ 2.36 (s, 3 H), 5.10 (d, J = 4.8 Hz, 2 H), 5.88 (s, 1 H), 5.88–6.12 (m, 1 H).

5h: mp 189.8 °C (*n*-hexane–acetone); ^{1}H NMR ($CDCl_3$) δ 2.22 (s, 3 H), 5.03 (d, J = 6.0 Hz, 2 H), 5.87 (s, 1 H), 5.88–6.12 (m, 1 H).

Isomerization of 4a and 5a with Pd(II) Salt. Treatment of **4a** (84 mg, 0.5 mmol) with $PdCl_2(PhCN)_2$ (4 mg, 0.01 mmol) in refluxing THF (2.5 mL) for 6 h resulted in a complete recovery of the starting material as judged from ^{1}H NMR and TLC monitoring. Under the similar conditions, **5a** afforded the same result.

Isomerization of 4c and 5c. (A) Isomerization of 4c with Pd(II) Salt. A mixture of **4c** (46 mg, 0.25 mmol) and $PdCl_2(PhCN)_2$ (10 mg, 0.025 mmol) in THF (2 mL) was heated under reflux for 4 h. ^{1}H NMR and TLC analyses showed the formation of **5c** as a main product with a small amount of the starting material **4c**. When the reaction was conducted at 25 °C for 28 h, only **4c** was obtained.

(B) Isomerization of 5c with Pd(II) Salt. Treatment of **5c** (182 mg, 1 mmol) and $PdCl_2(PhCN)_2$ (15 mg, 0.04 mmol) in

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refluxing THF (5 mL) for 4 h resulted in a complete recovery of **5c**, which was indicated by ^{1}H NMR and TLC monitoring of the reaction mixture.

(C) Thermal Isomerization of 4c. Heating a solution of **4c** (36 mg, 0.2 mmol) in THF (2 mL) gave a complete recovery of the starting material, as judged from ^{1}H NMR and TLC.

Isomerization of 4h with Pd(II) Salt. A solution of **4h** (92 mg, 0.5 mmol) and $PdCl_2(PhCN)_2$ (19 mg, 0.05 mmol) in THF (5 mL) was stirred under reflux for 4 h. After evaporation of the solvent, the residue was directly subjected to a column chromatography (silica gel, *n*-hexane–ethyl acetate gradient) to give **5h** (59 mg), **3h** (7 mg), and **4h** (26 mg). The isotopic purity of **3h**, **4h**, and **5h** was calculated to be greater than 97% on the basis of ^{1}H NMR area intensities.

S-Methylation of 4 or 5 (6 or 10). General Procedure. Into a stirred solution of sodium (25 mg, 1.1 mmol) in MeOH (5 mL) was added **4** or **5** (1 mmol) at room temperature. After 5 min, the reaction mixture was treated with methyl iodide (81 μL, 1.3 mmol) and was stirred at the same temperature overnight. Usual extractive workup with $CHCl_3$ and removal of the solvent gave crude **6** or **10**, which was purified by column chromatography [silica gel, $CHCl_3$–MeOH gradient (**6a**), *n*-hexane–ethyl acetate gradient (**10a**), *n*-hexane–acetone gradient (**6b,c,e, 10b–d,f**)] to yield pure **6** or **10**. Analytically pure materials were obtained by recrystallization (**6a–c,e, 10b**) or by distillation (**10a,c,d,f**).

6a: mp 79.4 °C (*n*-hexane–acetone); ^{1}H NMR ($CDCl_3$) δ 2.53 (s, 3 H), 4.40 (d, J = 5.4 Hz, 2 H), 4.96–5.40 (m, 2 H), 5.53–6.15 (m, 1 H), 5.94 (d, J = 7.5 Hz, 1 H), 7.15 (d, J = 7.5 Hz, 1 H).

10a: bp 110–112 °C (0.4 mmHg); ^{1}H NMR ($CDCl_3$) δ 2.51 (s, 3 H), 4.60 (d, J = 5.4 Hz, 2 H), 4.94–5.43 (m, 2 H), 5.49–6.10 (m, 1 H), 6.08 (d, J = 6.3 Hz, 1 H), 7.62 (d, J = 6.3 Hz, 1 H).

6b: mp 111.5 °C (*n*-hexane–acetone); ^{1}H NMR ($CDCl_3$) δ 1.94 (s, 3 H), 2.56 (s, 3 H), 4.36 (d, J = 5.4 Hz, 2 H), 4.97–5.40 (m, 2 H), 5.53–6.13 (m, 1 H), 6.99 (s, 1 H).

10b: mp 55.1 °C (*n*-hexane); ^{1}H NMR ($CDCl_3$) δ 1.99 (s, 3 H), 2.48 (s, 3 H), 4.61 (d, J = 5.4 Hz, 2 H), 4.93–5.32 (m, 2 H), 5.51–6.13 (m, 1 H), 7.54 (s, 1 H).

6c: mp 110.6 °C (*n*-hexane–acetone); ^{1}H NMR ($CDCl_3$) δ 2.22 (s, 3 H), 2.51 (s, 3 H), 4.45–4.62 (m, 2 H), 5.06–5.34 (m, 2 H), 5.53–6.14 (m, 1 H), 5.80 (s, 1 H).

10c: bp 125–130 °C (1.1 mmHg); ^{1}H NMR ($CDCl_3$) δ 2.18 (s, 3 H), 2.51 (s, 3 H), 4.57 (d, J = 4.8 Hz, 2 H), 4.93–5.31 (m, 2 H), 5.48–6.12 (m, 1 H), 5.94 (s, 1 H).

10d: bp 118–120 °C (0.28 mmHg); ^{1}H NMR ($CDCl_3$) δ 1.18 (d, J = 6.9 Hz, 6 H), 2.52 (s, 3 H), 2.32–3.01 (m, 1 H), 4.64 (d, J = 5.4 Hz, 2 H), 5.02–6.40 (m, 2 H), 5.60–6.23 (m, 1 H), 6.03 (s, 1 H).

6e: mp 112.4 °C (*n*-hexane–acetone); ^{1}H NMR ($CDCl_3$) δ 1.48 (d, J = 6.6 Hz, 3 H), 2.54 (s, 3 H), 4.71–5.46 (m, 3 H), 5.60–6.11 (m, 1 H), 5.96 (d, J = 7.2 Hz, 1 H), 7.15 (d, J = 7.2 Hz, 1 H).

10f: bp 112–115 C° (0.4 mmHg); ^{1}H NMR ($CDCl_3$) δ 1.62 (d, J = 7.2 Hz, 3 H), 2.14 (s, 3 H), 2.50 (s, 3 H), 5.02–5.36 (m, 3 H), 5.93 (s, 1 H), 5.97–6.56 (m, 1 H).

1-Allyluracil (7). (A) From 6a. A solution of **6a** (417 mg, 2.29 mmol) in 35% HCl (2 mL) and EtOH (4 mL) was heated under reflux for 3 h. After removal of the solvent, the residue was directly subjected to a column chromatography (silica gel, *n*-hexane–acetone gradient) to afford **7** (313 mg, 90% yield). Analytically pure sample was obtained by recrystallization from *n*-hexane–acetone: mp 109.9 °C; ^{1}H NMR ($CDCl_3$) δ 4.28 (d, J = 5.4 Hz, 2 H), 4.78–5.36 (m, 2 H), 5.50–5.97 (m, 1 H), 5.65 (d, J = 7.5 Hz, 1 H), 7.06 (d, J = 7.5 Hz, 1 H), 9.65 (br s, 1 H).

(B) From 8. To a suspension of NaH (0.42 g, 62.7% assay, 10.7 mmol) in DMF (40 mL) was added **8** (1.28 g, 8.9 mmol) at room temperature. After stirring for 30 min at the same temperature, allyl bromide (1.02 mL, 12 mmol) was added. The reaction mixture was heated at 80 °C for 1 h. Usual extractive workup with $CHCl_3$ and removal of the solvent provided crude **9**, which was purified by column chromatography (silica gel, *n*-hexane–acetone gradient) to give the spectroscopically pure compound **9** (1.09 g, 67% yield). Analytically pure material was obtained by recrystallization from *n*-hexane–acetone: mp 76.2 °C; ^{1}H NMR ($CDCl_3$) δ 3.53 (s, 3 H), 4.41 (d, J = 6.0 Hz, 2 H), 5.00–5.40 (m, 2 H), 5.60–7.03 (m, 1 H), 6.12 (d, J = 7.2 Hz, 1 H), 7.22 (d, J = 7.2 Hz, 1 H). Similarly, treatment of **9** (0.91 g, 5 mmol) with concentrated HCl provided **7** (0.74 g, 97% yield).

2-(Methylthio)-3-allylpyrimidin-4(3*H*)-one (10a) from 11. The procedure used to make **9** from **8** was applied. Treatment of **11** (1.42 g, 10 mmol) with allyl bromide (1.11 ml, 13 mmol) and column purification gave **10a** (0.74 g, 41% yield).

Iodo Thiol Imino Lactonization of 4 or 5. General Procedure. To a mixture of **4** or **5** (1 mmol) in H_2O (0.18 mL, 10 mmol) and DME (5 mL) was added iodine (279 mg, 1.1 mmol) and the solution was stirred at room temperature for 2 days. After treatment with aqueous $Na_2S_2O_3$, the product was thoroughly extracted with $CHCl_3$ (30 mL × several times). Removal of the solvent afforded **12** or **13** as a nice crystalline solid. Analytically pure sample was obtained by recrystallization.

12a: mp 164 – 166 °C dec (EtOH); ^{1}H NMR (Me_2SO-d_6) δ 3.57–3.74 (m, 2 H), 4.09–4.52 (m, 3 H), 5.87 (d, J = 7.2 Hz, 1 H), 7.83 (d, J = 7.2 Hz, 1 H).

12b: mp 177–180 °C dec (EtOH); ^{1}H NMR (Me_2SO-d_6) δ 1.78 (s, 3 H), 3.59–3.84 (m, 2 H), 4.11–4.56 (m, 3 H), 7.73 (s, 1 H).

12e: recrystallized from EtOH; mp 167–168 °C dec, 178–179 °C dec (these melting points are probably due to two diastereomers); ^{1}H NMR ($CDCl_3$) δ 1.48–1.66 (m, 3 H), 3.33–3.72 (m, 3 H), 4.48–4.84 (m, 1 H) 5.99–6.14 (m, 1 H), 7.32–7.48 (m, 1 H).

13c: mp 124.5 °C (*n*-hexane–acetone); ^{1}H NMR ($CDCl_3$) δ 2.38 (s, 3 H), 3.4–3.60 (m, 2 H), 3.94–4.37 (m, 1 H), 4.40–4.56 (m, 2 H), 6.03 (s, 1 H).

Registry No. **3a**, 31170-22-6; **3b**, 94731-76-7; **3c**, 62459-06-7; **3d**, 94731-77-8; **3e**, 94731-78-9; **3f**, 94731-79-0; **3g**, 94731-80-3; **3h**, 94731-81-4; **4a**, 89693-81-2; **4b**, 94731-82-5; **4c**, 94731-83-6; **4d**, 94731-84-7; **4e**, 94731-85-8; **4h**, 94731-90-5; **5a**, 94731-86-9; **5b**, 94731-87-0; **5c**, 60478-14-0; **5d**, 94731-88-1; **5f**, 94731-89-2; **5h**, 94731-91-6; **6a**, 6204-00-8; **6b**, 94731-92-7; **6c**, 94750-88-6; **6e**, 94731-93-8; **7**, 25855-26-9; **8**, 35551-31-6; **9**, 94731-99-4; **10a**, 94731-94-9; **10b**, 94731-95-0; **10c**, 94731-96-1; **10d**, 94731-97-2; **10f**, 94731-98-3; **11**, 5751-20-2; **12a**, 94732-00-0; **12b**, 94732-01-1; **12e** (isomer 1), 94732-02-2; **12e** (isomer 2), 94732-04-4; **13c**, 94732-03-3; 6-isopropyl-2-thiouracil, 28456-53-3; 2-propenyl-*1,1*-d_2 chloride, 37730-14-6; 2-propen-1-ol-*1,1*-d_2, 10475-51-1; 2-thiouracil, 141-90-2; 5-methyl-2-thiouracil, 636-26-0; 6-methyl-2-thiouracil, 56-04-2; allyl bromide, 106-95-6; *trans*-crotyl bromide, 29576-14-5; methallyl chloride, 563-47-3; $PdCl_2(PhCN)_2$, 14220-64-5.

Supplementary Material Available: Table listing the IR and mass spectra and physical data (3 pages). Ordering information is given on any current masthead page.