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Ring cleavage of dihydropyrimidine skeleton

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ABSTRACT

The first observation of ring cleavage between positions 1 and 2 of a 1,4-dihydropyrimidine skeleton was reported upon the nucleophic addition of 4,6-unsubstituted 1,4-dihydropyrimidine with 3 equiv of an aniline derivative or phenylhydrazine in the presence of 0.1 equiv of pyridinium *p*-toluenesulfonate (PPTS) in CH_2Cl_2; the nucleophilic reactions of 4-methyl-6-unsubstituted 1,6(3,4)-dihydropyrimidine with the same amines gave conventional substituted products at position 2. The effect of this ring opening was found to be due to the electron density of the benzene ring of a nucleophilic amine. On the other hand, aralkylamines, alkylamines, or heterocyclic amines did not cleave the skeleton. The ring-opening chemical structure was confirmed by X-ray crystallographic analysis. This characteristically different phenomenon may be due to the pattern of two C=C double bonds of 1,4-DP and 1,6(3,4)-DP as well as to the effect of two substituted groups on the DP ring.

Dihydropyrimidine (DP) could be theoretically represented as nine isomers including tautomers when it has different substituted groups.[1] Moreover, DPs in some cases are spontaneously oxidized during isolation or storage. Therefore, they are unstable and sometimes difficult to handle. The Weis, Cho, Kappe, and Atwal groups reported the synthesis of a series of 1,4(3,4)-dihydropyrimidines (tautomeric mixture) (Fig. 1).[1,2] Recently, we have disclosed excellent results of nucleophilic substitution at position 2 of 1-*tert*-butyl 5-ethyl 4-methyl-2-methylsulfanyl-1,6-dihydropyrimidine-1,5-di carboxylate **1**, although substitution at position 2 of DPs has been difficult because of low reactivity at the position.[3] In this Letter, a variety of DPs **a** were obtained in excellent yields. (Scheme 1, Eq. 1) In contrast, a series of substitutions at position 2 of 1-*tert*-butyl 5-ethyl 2-methylsulfanyl-1,4-dihydropyrimidine-1,5-dicarboxylate **2** did not afford the desired compounds, but provided an unusual compound whose structure could not be determined at that time. Since then, we have studied the difference in the reactivity between DP **1** and **2**. In this work, we clarified the surprising result that the dihydropyrimidine skeleton was cleaved to a linear compound in good yield instead of giving 2-aminodihydropyrimidine **b**.

Generally, most heterocyclic rings cannot be easily cleaved. [4] No report has been found on ring-opening reactions of the dihydropyrimidine skeleton, although the skeleton is sometimes oxidized to a pyrimidine skeleton.

Initially, we assumed that the alkoxycarbonylation of compound **c** with Boc_2O occurred at position 3 to provide the

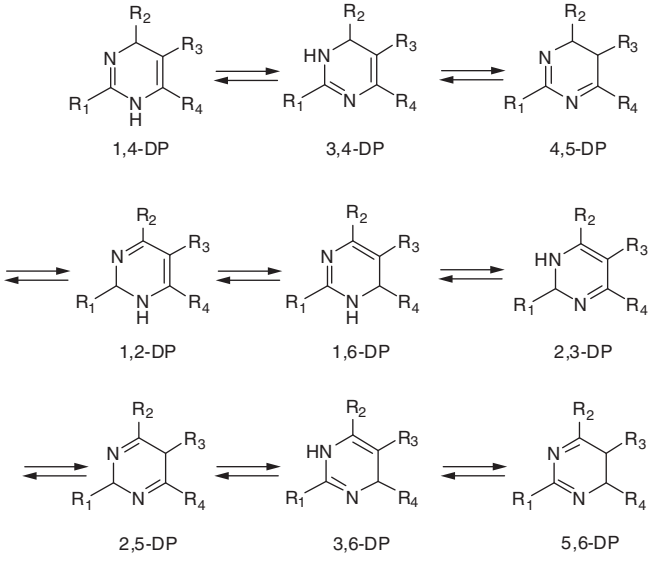

Figure 1. Isomerization and tautomerism of dihydropyrimidines.

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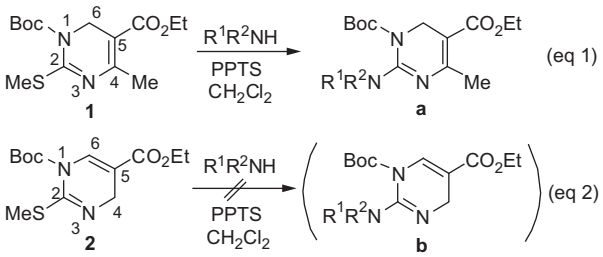
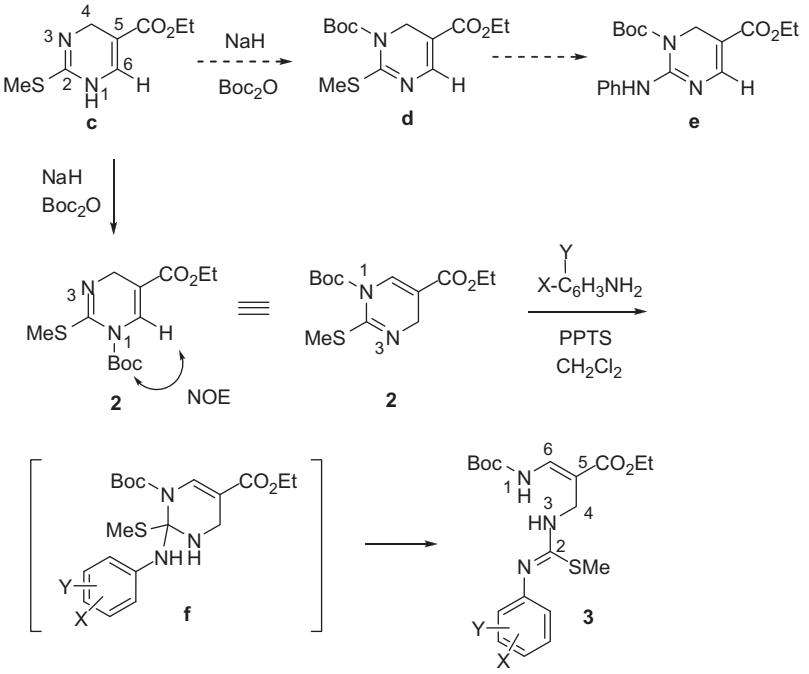


Scheme 1. Difference in nucleophilic substitution between dihydropyrimidines.

compound **d**[2a] and that the successive nucleophilic addition of an amine should afford the compound **e**. However, the NMR characterization of the chemical structure of the alkoxycarbonylated compound did not indicate **d** but rather compound **2** because of the observation of 1.4% NOE between the olefin proton and the *t*-Bu protons of the Boc group.

Therefore, the position of the protecting group was proved to be the other position. Thus, the nucleophilic reaction of DP **2** with 3 equiv of aniline in the presence of 0.1 equiv of pyridinium *p*-toluenesulfonate (PPTS) in CH_2Cl_2 was carried out at room temperature for 9 h to give an unidentified solid compound as the sole product in a 65% yield.[5] The ^1H NMR of the product was not what was expected for **b**; both methylthio and phenylamino groups were clearly present. However, this could not be assigned to the chemical structure of **f** (Scheme 2). Therefore, X-ray crystallographic analysis was performed. To our surprise, the ORTEP drawing of the compound revealed the chemical structure of (*E*)-ethyl 3-*tert*-butoxycarbonylamino-2-[(*Z*)-2-methyl-3-phenylisothioureido-methyl]acrylate **3a**, the result of the ring cleavage of the dihydropyrimidine skeleton (Fig. 2).[6]



Scheme 2. Unusual ring cleavage of dihydropyrimidine skeleton with amine.

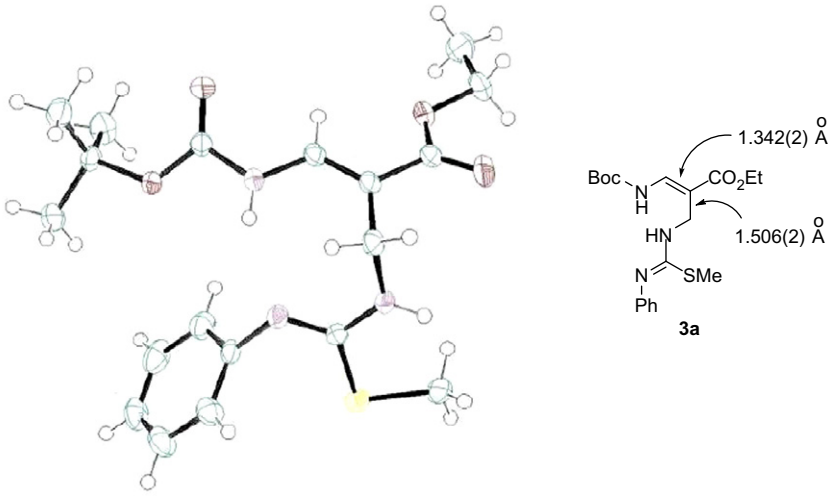


Figure 2. ORTEP drawing of **3a** with probability ellipsoids drawn at 50% level.

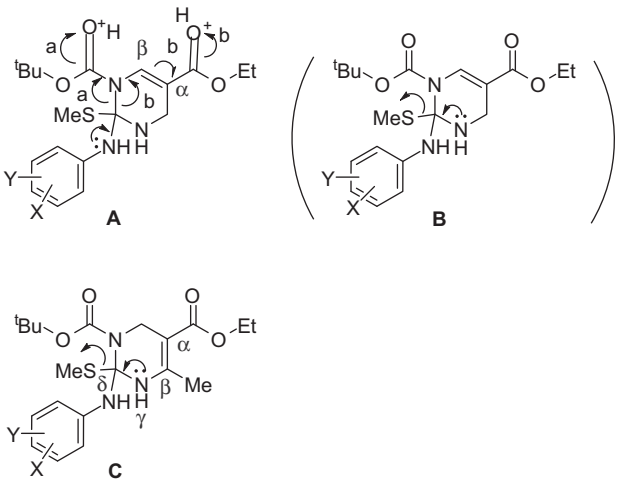
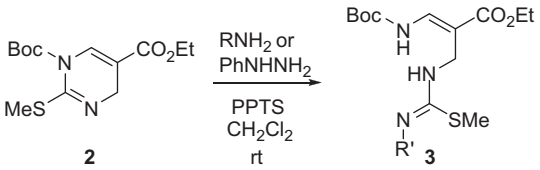


Figure 3. Elimination by effect of α,β-unsaturated ester group and/or Boc group.

Table 1
Results of ring cleavage of dihydropyrimidine skeleton



Entry	Amine or hydrazine	Time (h)	Product	Yield (%)
1	$C_6H_5NH_2$	9	**3a**	65
2	4-$MeOC_6H_4NH_2$	6	**3b**	95
3	4-$MeC_6H_4NH_2$	24	**3c**	78
4	2-$MeC_6H_4NH_2$	24	**3d**	24
5	3,4-di(MeO)$C_6H_3NH_2$	24	**3e**	88
6	$C_6H_5NHNH_2$	12	**3f**	24

*R′ = R or PhNH (in compound **3**).

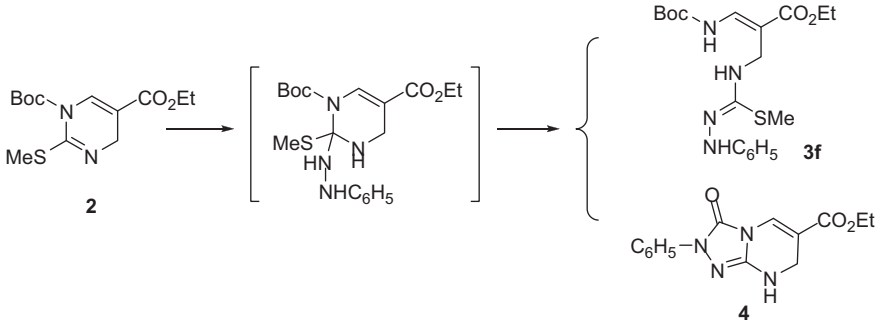
The ORTEP drawing of **3a** confirmed that the position of the Boc group was not N-3 but N-1, and that the location of the double bond was as shown in Figure 2, determined by comparing two bond lengths [1.342(2) angstroms (C=C) and 1.506(2) angstroms (C–C)].

Thus, the reaction proceeded not as in B but as in A (Fig. 3) to yield the ring-opening compound **3**, presumably by the effect of an α,β-unsaturated ester group and/or a Boc group. On the other hand, it is assumed that, in the case of reactions of the compound **1** with amines, elimination occurred to afford the compound **a** (Scheme 1) so that a product as shown in C in Figure 3 generated α,β-and γ,δ-conjugated double bonds.

Subsequently, we examined the generality of the ring cleavage reaction of a dihydropyrimidine skeleton. Under the same reaction conditions, a variety of amines and hydrazine were subjected to the reactions, such as 4-methoxyaniline, 4-nitroaniline, 4-methylaniline, 3,4-dimethoxyaniline, benzylamine, *n*-hexylamine, phenylhydrazine, 2-aminothiazole and 2-aminoimidazole. The results are shown in Table 1.

Thus, ethyl 3-*tert*-butoxycarbonylamino-2-[3-(4-methoxyphenyl)-2-methylisothioureidomethyl]acrylate **3b** and ethyl 3-*tert*-butoxycarbonylamino-2-[3-(3,4-dimethoxyphenyl)-2-methylisothioureidomethyl]acrylate **3e** were obtained in 95% and 88% yields, respectively, without the recovery of the starting material **2** (entries 2 and 5). In contrast to these results, 4-nitroaniline with an electron-withdrawing group did not cleave the dihydropyrimidine ring, but the starting material was recovered. Therefore, it was clarified that the electron density in the benzene ring (nucleophilicity of the amines) plays a crucial role in the unusual cleavage reaction. The ring-opening reaction did not proceed to completion using 2-methylaniline presumably because of the steric hindrance of the methyl group (entry 4). Aralkylamines or alkylamines, such as benzylamine or *n*-hexylamine, as well as heterocyclic amines, 2-aminothiazole or 2-aminoimidazole, were subjected to the reaction. However, they did not furnish the linear compound **3** but led to the recovery of the compound **2**, because the nitrogen atom of an aralkylamine and an alkylamine may be protonated by PPTS and have its nucleophilicity diminished. Subsequently, we studied phenylhydrazine instead of amines as the nucleophile and found that it also cleaved the dihydropyrimidine ring to afford the compound **3f** in 34% yield, accompanied by the substituted and cyclized product, ethyl 3-oxo-2-phenyl-2,3,7,8-tetrahydro[1,2,4]triazolo-[4,3-*a*]pyrimidine-6-carboxylate **4** in 8% yield and the recovery of **2** in 32% yield (Scheme 3).

In summary, nucleophilic reactions of the dihydropyrimidines **1** and **2** with amines or phenylhydrazine provided the markedly different results described. This result is due to the difference in pattern between the two C=C double bonds of 1,4-DP and 1,6(3,4)-DP as well as to the effect of two substituted groups on the DP ring shown in Figure 3. Consequently, a novel cleavage reaction of 1,4-dihydropyrimidine skeleton was observed, although 1,4-DP is usually more stable than 1,6(3,4)-DP. In addition, the effect of this ring opening was found to be due to the electron density of the benzene ring of nucleophilic amines. Our findings may serve future research on dihydroheterocycles as well as on dihydropyrimidines.



Scheme 3. Unusual ring cleavage of dihydropyrimidine skeleton with phenylhydrazine and preparation of bicyclic compound **4**.

Acknowledgments

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Supplementary data

Supplementary data (NMR, IR, MS spectra of products **3** and **4**, and X-ray data of **3a**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.10.130.

References and notes

1. (a) Traube, W.; Schwarz, R. *Chem. Ber.* **1899**, *32*, 3163–3174; (b) Weis, A. L. *Tetrahedron Lett.* **1982**, *23*, 449–452; (c) Weis, A. L.; van der Plas, H. C. *Heterocycles* **1986**, *24*, 1433–1455; (d) Cho, H.; Iwashita, T.; Ueda, M.; Mizuno, A.; Mizukawa, K.; Hamaguchi, M. *J. Am. Chem. Soc.* **1988**, *110*, 4832–4834; (e) Wendelin, W.; Schermanz, K. *J. Heterocycl. Chem.* **1984**, *21*, 65–69.
2. (a) Cho, H.; Shima, K.; Hayashimatsu, M.; Ohnaka, Y.; Mizuno, A.; Takeuchi, Y. *J. Org. Chem.* **1985**, *50*, 4227–4230; (b) Cho, H.; Ohnaka, Y.; Hayashimatsu, M.; Ueda, M.; Shima, K. *Tetrahedron Lett.* **1986**, *27*, 6377–6380; (c) Cho, H.; Mizuno, A.; Shima, K.; Ueda, M.; Takeuchi, Y.; Hamaguchi, M.; Taniguchi, N. *Heterocycles* **1988**, *27*, 769–774; (d) Weis, A. L. *Synthesis* **1985**, 528–530; (e) Kashima, C.; Shimizu, M.; Katoh, A.; Omote, Y. *Tetrahedron Lett.* **1983**, *24*, 209–212; (f) Cho, H.; Takeuchi, Y.; Ueda, M.; Mizuno, A. *Tetrahedron Lett.* **1988**, *29*, 5405–5408; (g) Atwal, K. S.; Rovnyak, G. C.; O'Reilly, B. C.; Schwartz, J. *J. Org. Chem.* **1989**, *54*, 5898–5907; (h) Matloobi, M.; Kappe, C. O. *J. Comb. Chem.* **2007**, *9*, 275–284; (i) Kappe, C. O. *Tetrahedron* **1993**, *49*, 6937–6963; (j) Kappe, C. O. *Eur. J. Med. Chem.* **2000**, *35*, 1043–1052; (k) Kappe, C. O.; Stadler, A. *Org. React.* **2004**, *63*, 1–116; (l) Cho, H.; Ueda, M.; Shima, K.; Mizuno, A.; Hayashimatsu, M.; Ohnaka, Y.; Takeuchi, Y.; Hamaguchi, M.; Aisaka, K.; Hidaka, T.; Kawai, M.; Takeda, M.; Ishihara, T.; Funahashi, K.; Satoh, F.; Morita, M.; Noguchi, T. *J. Med. Chem.* **1989**, *32*, 2399–2406; (m) Atwal, K. S.; Rovnyak, G. C.; Kimball, S. D.; Floyd, D. M.; Moreland, S.; Swanson, B. N.; Gougoutas, J. Z.; Schwartz, J.; Smillie, K. M.; Malley, M. F. *J. Med. Chem.* **1990**, *33*, 2629–2635; (n) Rovnyak, G. C.; Atwal, K. S.; Hedberg, A.; Kimball, S. D.; Moreland, S.; Gougoutas, J. Z.; O'Reilly, B. C.; Schwartz, J.; Malley, M. F. *J. Med. Chem.* **1992**, *35*, 3254–3263; (o) Cho, H.; Yasui, Y.; Kobayashi, S.; Kwon, E.; Arisawa, M.; Yamaguchi, M. *Heterocycles* **2011**, *83*, 1807–1818.
3. Cho, H.; Nishimura, Y.; Yasui, Y.; Kobayashi, S.; Yoshida, S.; Kwon, E.; Yamaguchi, M. *Tetrahedron* **2011**, *67*, 2661–2669.
4. Acquadro, F.; Oulyadi, H.; Venturello, P.; Maddaluno, J. *Tetrahedron Lett.* **2002**, *43*, 8759–8763.
5. General procedure for the ring cleavage of dihydropyrimidine skeleton: A solution of dihydropyrimidine **2** (15.4 mg, 0.0513 mmol), aniline (13.8 μL, 14.1 mg, 0.151 mmol) and pyridinium *p*-toluenesulfonate (1.31 mg, 0.00522 mmol) in CH_2Cl_2 (1.0 mL) was stirred for 9 h at rt. The reaction mixture was quenched with water and the organic materials were extracted with EtOAc. The combined organic layer was washed with water and brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave the residue, which was purified by silica gel column chromatography (*n*-hexane:EtOAc = 10:0 → 8:2) to give **3a** (13.2 mg, 65%) as colorless needles; mp 132.2–133.5 °C (*n*-hexane); IR (KBr): 3388, 2981, 1731, 1685, 1651, 1566, 1508, 1490, 1234, 1155 cm^{1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.31 (9H, s, C*Me*$_3$), 1.31 (3H, t, *J* = 7.2 Hz, CH_2CH_3), 2.19 (3H, s, SCH_3), 4.21 (2H, q, *J* = 7.2 Hz, CH_2CH_3), 4.26 (2H, d, *J* = 6.4 Hz, CH_2NH), 5.17 (1H, t, *J* = 6.4 Hz, CH_2NH), 6.94 (2H, d, *J* = 8.0 Hz, Ar-*o*-*H*), 7.05 (1H, t, *J* = 8.0 Hz,, Ar-*p*-*H*), 7.26 (2H, d, *J* = 8.0 Hz, Ar-*m*-*H*), 7.98 (1H, d, *J* = 11.2 Hz, C*H*NH), 10.48 (1H, d, *J* = 11.2 Hz, CHN*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 14.4, 27.8, 38.0, 60.3, 81.3, 107.7, 123.0, 123.2, 128.6, 139.3, 148.3, 152.8, 155.5, 168.6; LRMS (EI) *m*/*z*: 393 (M^+); HRMS: calcd for $C_{19}H_{27}N_3O_4S$, 393.1722; found, 393.1727.
6. Crystallographic data for compound **3a** has been deposited with the Cambridge Crystallographic Data Centre (CCDC). The coordinates can be obtained on request from the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK. The CCDC Number of **3a** is 842456.