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IODOBENZENE DIACETATE–PROMOTED N–N AND N–O BOND FORMATION FOR PYRAZOLO- AND ISOXAZOLOPYRIMIDINE SYNTHESES

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Abstract – Pyrazolo[3,4-*d*]pyrimidine-4,6-dione derivatives were efficiently synthesized *via* the intramolecular N–N bond coupling of 5-iminomethyl-6-aminouracil derivatives using iodobenzene diacetate. The oxidative coupling was also applied to the analogous N–O bond formation producing isoxazolo[3,4-*d*]primidine-4,6-dione derivatives.

This paper is dedicated to the memory of Dr. John Daly.

INTRODUCTION

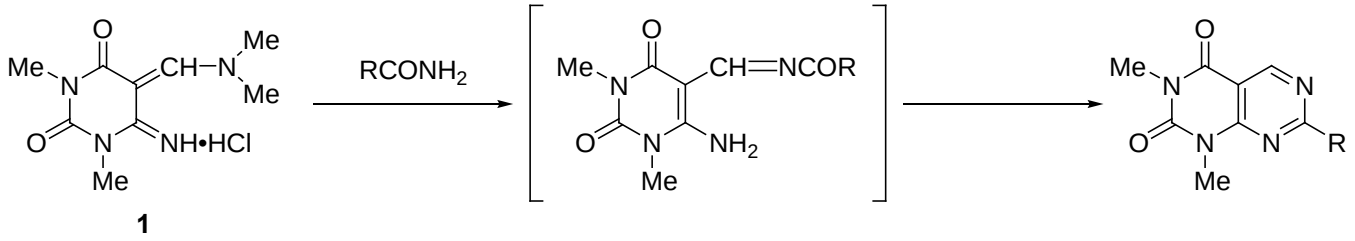
Since allopurinol, pyrazolo[3,4-*d*]pyrimidin-4-one, was developed as a clinical medicine for the treatment of hyperuricemia and gouty arthritic diseases based on the inhibition of xanthine oxidase,[1] much attention has been focused on the biological evaluation of the pyrazolo[3,4-*d*]pyrimidine derivatives.[2,3] Recent biological studies of such pyrazolopyrimidine derivatives have targeted a wide range of biomolecules, such as Src protein kinases,[4,5] EGF receptor tyrosine kinases,[6] Abelson kinase,[7] p38 MAP kinase,[8] cyclic cyclooxygenase-2,[9] bacterial DNA polymerase III,[10] mycobacterial lumazine synthase,[11] adenosine A_1 receptor,[12] cannabinoid receptor type 1,[13] etc. The synthetic methods for the construction of the pyrazolo[3,4-*d*]pyrimidine ring system have involved the cyclization of the pyrazole[5,7,8,12,14,15] or pyrimidine intermediates,[11,16] but the nitrogen–nitrogen (N–N) bond forming reaction was never used for the cyclization of a pyrazole ring until our published communication related to the iodobenzene diacetate-promoted N–N bond formation.[17] Although the isoxazolo[3,4-*d*]pyrimidine derivatives were structurally very similar to the pyrazolo[3,4-*d*]pyrimidine derivatives, they have been basically synthesized by the isoxazole ring formation starting from the 5,6-disubstituted pyrimidine derivatives,[18,19] and the ring closure reaction via the nitrogen–oxygen (N–O) bond formation appeared during the thermolysis of the 5-acyl-6-azidouracils[20,21] and photolysis of the 5-acyl-6-sulfiliminouracils.[22]

Hypervalent iodine reagents,[23] such as iodobenzene diacetate and phenyliodine bis(trifluoroacetate), have

been used for the oxidative N–N[17,24,25] and N–O[26] bond formations to build the pyrazolo- and isoxazoloarene motifs in past decade. We now describe the details of the iodobenzene diacetate-promoted cyclization method for the preparation of pyrazolo[3,4-*d*]pyrimidine-4,6-diones and isoxazolo[3,4-*d*]pyrimidine-4,6-diones via the N–N and N–O bond creation, respectively.

RESULTS AND DISCUSSION

During the course of our study on the fused pyrimidine synthesis, we found that 5-[(dimethylamino)methylene]dihydro-6-imino-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione hydrochloride (**1**), which was readily prepared by the reaction of the commercially available 6-amino-1,3-dimethyluracil with phosphoryl chloride in dimethylformamide (DMF), underwent a nucleophilic attack on the dimethylaminomethylene carbon at the 5-position of the pyrimidine ring by a nitrogen atom from a series of amides, and subsequent cyclization afforded the pyrimido[4,5-*d*]pyrimidine derivatives (Scheme 1).[27,28]



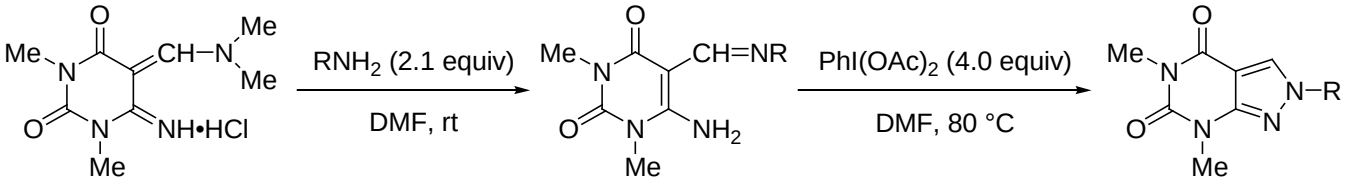
Scheme 1. Pyrimido[4,5-*d*]pyrimidine synthesis

When we used excess amounts of primary amines in place of the amides as nucleophiles, the 6-amino-5-(substituted iminomethyl)-1,3-dimethyluracil derivatives (**2**)[29] was stably obtained, which were used as starting materials for the intramolecular N–N bond formation (Table 1). The addition of a base, such as triethylamine (Et_3N) or lithium hydride (LiH), increased the reaction efficiency due to the enhanced nucleophilicity of the amine nitrogen atoms (Entries 1, 10–12); e.g., the use of *n*-butylamine could be reduced to 1.1 equiv by the addition of 1.1 equiv of Et_3N, while the reaction with 2.1 equiv of *n*-butylamine gave **2j** in only 31% yield (Entry 10).

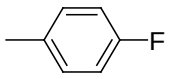
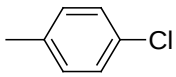
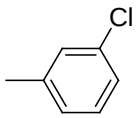
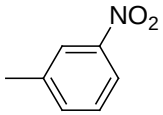
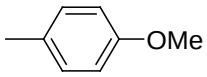
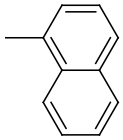
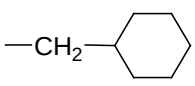
Our attempts of the intramolecular N–N bond formation were initiated by the investigation of some oxidants using **2a** as a substrate. While the use of 4 equiv of *N*-bromosuccinimide resulted in the formation of a complex mixture containing unreacted **2a**, the oxidation with 4 equiv of lead tetraacetate in DMF at rt gave the desired 5,7-dimethyl-2-phenylpyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (**3a**) in 47% yield. Furthermore, the employment of iodobenzene diacetate significantly improved the yield up to 87% (Entry 1). Therefore, we chose iodobenezene diacetate as the oxidant for the present cyclization. As shown in Entries 1–7, the 5-aryl substituted iminomethyluracil derivatives (R = aryl: **2a**–**2g**) were

smoothly oxidized to afford the desired pyrazolo[3,4-*d*]pyrimidine derivatives (**3a**–**3g**) in good to excellent yields. Although the 5-alkyl substituted iminomethyluracil derivatives (R = alkyl: **2h**–**2m**) were less reactive under the same reaction conditions, the addition of 2 equiv of LiH improved the N–N bond formation efficiency (Entries 9–13). For example, the yield of the *t*-butyl substituted pyrazolo[3,4-*d*]pyrimidine **3i** was improved from 35% to 56% (Entry 9).

Table 1. Synthesis of 2-substituted 5,7-dimethylpyrazolo[3,4-*d*]pyrimidine-4,6-diones



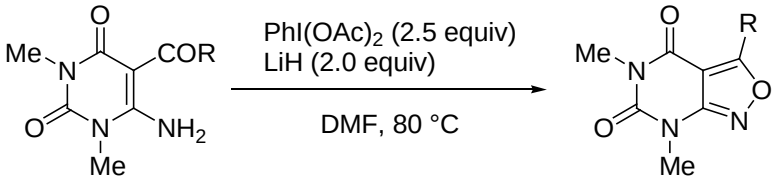
1 **2** **3**

Entry	R	Precursor	Yield (%)	Time (h)	Product	Yield (%)
1	Ph	**2a**	78[a]	1	**3a**	87 (47)[d]
2		**2b**	74	1	**3b**	92
3		**2c**	36	1	**3c**	76
4		**2d**	43	2	**3d**	80
5		**2e**	76	3	**3e**	55
6		**2f**	54	5	**3f**	40
7		**2g**	86	5	**3g**	97
8	Me	**2h**	89	3	**3h**	61
9	*t*-Bu	**2i**	60	4	**3i**	35, 56[e]
10	*n*-Bu	**2j**	31, 83[a]	2	**3j**	85[e]
11	*c*-Pent	**2k**	99[b]	2	**3k**	72[e]
12	*c*-Hex	**2l**	91[c]	1	**3l**	68[e,f]
13		**2m**	63	1	**3m**	67[e]

[a] 1.1 equiv of primary amine and 1.1 equiv of Et_3N were used. [b] 1.1 equiv of *c*-pentylamine and 1.1 equiv of LiH were used. [c] 1.2 equiv of *c*-hexylamine hydrochloride and 2.2 equiv of Et_3N were used. [d] Lead tetraacetate (4.0 equiv) was used as an oxidant instead of $PhI(OAc)_4$. [e] 2.0 equiv of LiH were added. [f] 2.5 equiv of iodobenzene diacetate were used.

We next explored the intramolecular N–O bond forming reaction using the 5-acyl-substituted 6-amino-1,3-dimethyl-2,4-pyrimidinedione derivatives (**4a**–**4c**) by iodobenzene diacetate (Table 2). The oxidative cyclization in the presence of 2 equiv of LiH was successfully achieved to give the corresponding 3-substituted 5,7-dimethylisoxazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione derivatives (**5a**–**5c**) in good to excellent yields.

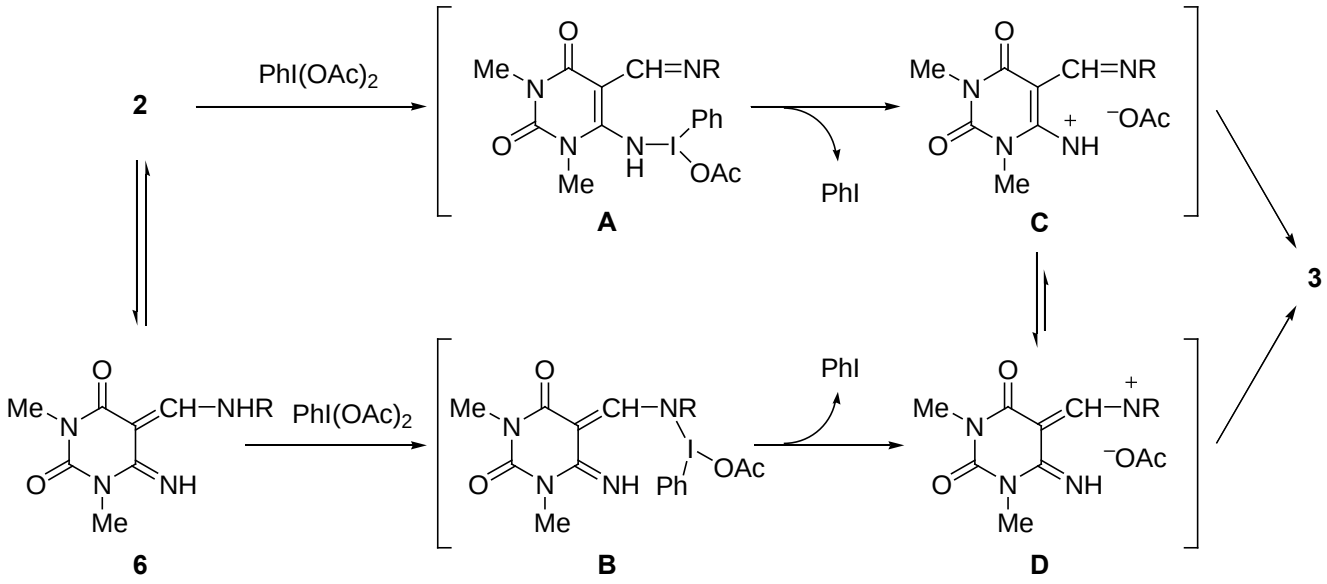
Table 2. Synthesis of isoxazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-diones by the N–O bond formation



4a–**4c** **5a**–**5c**

Entry	Substrate	R	Time (h)	Product	Yield (%)
1	**4a**	Me	4	**5a**	82
2	**4b**	Et	3	**5b**	72
3	**4c**	*n*-Pr	0.5	**5c**	94

A plausible mechanism for the intramolecular N–N bond formation is depicted in Scheme 2. The oxidation would be initiated by the reaction of the iodobenzene diacetate with the amine nitrogen of **2** or/and its tautomer, 6-aminomethylidene-6-iminouracil (**6**). Iodobenzene would be dissociated from the resulting intermediates **A** and **B** to give the corresponding nitrenium acetate ion pairs **C** and **D**, respectively. Nitrenium ions are highly electrophilic and stabilized by the neighboring electron-donating group such as aryl, alkoxy, and amino groups.[25,30] In this study, the 5-arylimino-substituted uracils were rather reactive compared with the 5-alkylimino-substituted uracils, and the reaction was promoted in the presence of LiH (Table 1). Therefore, the more stable nitrenium ion **D** could be favorably formed and attacked by the lone pair of the 6-imino nitrogen atom, the nucleophilicity of which would be enhanced under the basic conditions.



Scheme 2. Plausible reaction mechanism

CONCLUSION

We have developed a facile synthetic method for the construction of a variety of pyrazolo[2,3-*d*]pyrimidine and isoxazolo[2,3-*d*]pyrimidine derivatives by the iodobenzene diacetate-promoted oxidative N–N or N–O bond formation. The oxidant is relatively less toxic and produces no hazardous inorganic wastes. Since such fused pyrimidine analogs have recently attracted attention as target molecules for drug development, the present study would offer a facile and safe synthetic approach to potential bioactive compounds.

EXPERIMENTAL

General Methods. Unless otherwise stated, the commercially obtained materials were used without further purification. The ^{1}H NMR spectra were recorded by a JEOL JNM EX-400 spectrometer. Chemical shifts (δ) are expressed in ppm and internally referenced (0.00 ppm for tetramethylsilane-$CDCl_3$ and 2.49 ppm for DMSO-d_6). The EI mass spectra were obtained using a JEOL JMS-SX102A instrument. The elemental analyses were performed by a YANACO MT-5 instrument. The flash column chromatography was performed using Kanto Chemical Co., Inc., silica gel 60N, spherical neutral (63-210 μm).

Synthesis of substrate:

General preparation method of 6-amino-5-[(substituted)-iminomethyl]-1,3-dimethyluracil derivatives (2a–2m). To a suspension of 5-[(dimethylamino)methylene]dihydro-6-imino-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione hydrochloride

(**1**) (2.47 g, 10.0 mmol) in dry DMF (70 mL) was dropwise added an amine (21.0 mmol). After stirring at rt for 12 h, the mixture was concentrated *in vacuo*. The residue was triturated with Et_2O (20 mL), and the resulting precipitate was collected on a Kiriyama funnel and then recrystallized from EtOH.

6-Amino-1,3-dimethyl-5-[(phenylimino)methyl]uracil (2a)[29]**:** Aniline (1.0 mL, 11.0 mmol) and Et_3N (1.5 mL, 10.8 mmol) were added to a suspension of **1** (2.47 g, 10.0 mmol) in DMF (20 mL). mp 259–160 °C. ^{1}H NMR (DMSO-d_6) δ 3.22 (3H, s), 3.39 (3H, s), 7.27 (5H, m), 8.34 (1H, br s), 8.76 (1H, s), 11.11 (1H, br s). MS (EI) *m*/*z*: 258 (M^+). *Anal.* Calcd for $C_{13}H_{14}N_4O_2$: C, 60.45; H, 5.46; N, 21.70. Found: C, 60.64; H, 5.55; N, 21.67.

6-Amino-5-[{(4-fluorophenyl)imino}methyl]-1,3-dimethyluracil (2b)[17]**:** mp 288–290 °C (recrystallized from EtOH). ^{1}H NMR (DMSO-d_6) δ 3.17 (3H, s), 3.35 (3H, s), 7.16 (2H, m), 7.17 (2H, m), 8.31 (1H, br s), 8.68 (1H, s), 10.99 (1H, br s). MS (EI) *m*/*z*: 276 (M^+). *Anal.* Calcd for $C_{13}H_{13}FN_4O_2$: C, 56.50; H, 4.75; N, 20.29. Found: C, 56.33; H, 4.72; N, 20.30.

6-Amino-5-[{(4-chlorophenyl)imino}methyl]-1,3-dimethyluracil (2c)[17]**:** mp 258–259 °C (recrystallized from EtOH). ^{1}H NMR ($CDCl_3$) δ 3.39 (3H, s), 3.49 (3H, s), 5.50 (1H, br s), 7.10 (2H, d, *J* = 8.8 Hz), 7.31 (2H, d, *J* = 8.8 Hz), 8.80 (1H, s), 11.95 (1H, br s). MS (EI) *m*/*z*: 292 (M^+). *Anal.* Calcd for $C_{13}H_{13}ClN_4O_2$: C, 53.34; H, 4.48; N, 19.14. Found: C, 53.48; H, 4.59; N, 19.22.

6-Amino-5-[{(3-chlorophenyl)imino}methyl]-1,3-dimethyluracil (2d)[17]**:** mp 265–267 °C (recrystallized from EtOH). ^{1}H NMR (DMSO-d_6) δ 3.18 (3H, s), 3.36 (3H, s), 7.10 (1H, d, *J* = 8.3 Hz), 7.15–7.22 (2H, m), 7.38 (1H, t, *J* = 8.3 Hz), 8.38 (1H, br s), 8.70 (1H, s), 10.90 (1H, br s). MS (EI) *m*/*z*: 292 (M^+). *Anal.* Calcd for $C_{13}H_{13}ClN_4O_2$: C, 53.34; H, 4.48; N, 19.14. Found: C, 53.15; H, 4.46; N, 19.21.

6-Amino-1,3-dimethyl-5-[{(3-nitrophenyl)imino}methyl]uracil (2e)[17]**:** mp >300 °C. ^{1}H NMR (DMSO-d_6) δ 3.19 (3H, s), 3.37 (3H, s), 7.59–7.66 (2H, m), 7.92 (1H, s), 7.96–8.01 (1H, m), 8.46 (1H, br s), 8.79 (1H, s), 10.87 (1H, br s). MS (EI) *m*/*z*: 303 (M^+). *Anal.* Calcd for $C_{13}H_{13}N_5O_4$: C, 51.48; H, 4.32; N, 23.09. Found: C, 51.25; H, 4.33; N, 23.08.

6-Amino-5-[{(4-methoxyphenyl)imino}methyl]-1,3-dimethyluracil (2f)[17]**:** mp 212–214 °C (recrystallized from EtOH). ^{1}H NMR ($CDCl_3$) δ 3.38 (3H, s), 3.48 (3H, s), 3.82 (3H, s), 5.54 (1H, br s), 6.91 (2H, d, *J* = 8.8 Hz), 7.14 (2H, d, *J* = 8.8 Hz), 8.86 (1H, s), 12.23 (1H, br s). MS (EI) *m*/*z*: 288 (M^+). *Anal.* Calcd for $C_{14}H_{16}N_4O_3$: C, 58.32; H, 5.59; N, 19.44. Found: C, 58.17; H, 5.56; N, 19.38.

6-Amino-1,3-dimethyl-5-[(1-naphthalenylimino)methyl]uracil (2g)[17]**:** mp 275–278 °C. ^{1}H NMR ($CDCl_3$) δ 3.41 (3H, s), 3.54 (3H, s), 5.64 (1H, br s), 7.12 (1H, d, *J* = 7.8 Hz), 7.43–7.55 (3H, m), 7.69 (1H, d, *J* = 8.3 Hz), 7.86 (1H, d, *J* = 8.3 Hz), 8.17 (1H, d, *J* = 7.8 Hz), 8.99 (1H, s), 12.25 (1H, br s). MS (EI) *m*/*z*: 308 (M^+). *Anal.* Calcd for $C_{17}H_{16}N_4O_2$: C, 66.22; H, 5.23; N, 18.17. Found: C, 66.12; H, 5.27; N, 18.13.

6-Amino-1,3-dimethyl-5-[(methylimino)methyl]uracil (2h)[29]**:** mp 232–233 °C (recrystallized from MeOH). ^{1}H NMR ($CDCl_3$) δ 3.28 (3H, s), 3.32 (3H, s), 3.36 (3H, s), 8.33 (1H, s). MS (EI) *m*/*z*: 196 (M^+). HRMS (EI) Calcd for $C_8H_{12}N_4O_2$ (M^+) 196.0960. Found 196.0972.

6-Amino-5-[(*t*-butylimino)methyl]-1,3-dimethyluracil (2i): mp 186 °C. ^{1}H NMR ($CDCl_3$) δ 1.39 (9H, s), 3.32 (3H, s), 3.33 (3H, s), 8.39 (1H, s). MS (EI) *m*/*z*: 238 (M^+). *Anal.* Calcd for $C_{11}H_{18}N_4O_2$: C, 55.45; H, 7.61; N, 23.51. Found: C, 55.22; H, 7.52; N, 23.25.

6-Amino-5-[(butylimino)methyl]-1,3-dimethyluracil (2j)[31]**:** *n*-Butylamine hydrochloride (1.22 g, 11.0 mmol) and Et_3N (1.5 mL, 10.8 mmol) were added to a suspension of **1** (2.47 g, 10.0 mmol) in DMF (50 mL). mp 171–172 °C. ^{1}H NMR ($CDCl_3$) δ 0.95 (3H, t, *J* = 7.0 Hz), 1.40 (2H, m), 1.62 (2H, m), 3.32 (3H, s), 3.35 (3H, s), 3.46 (2H, t, *J* = 7.0 Hz), 6.30 (1H, br s), 8.30 (1H, s), 11.90 (1H, br s). MS (EI) *m*/*z*: 238 (M^+). *Anal.* Calcd for $C_{11}H_{18}N_4O_2$: C, 55.45; H, 7.61; N, 23.51. Found: C, 55.20; H, 7.52; N, 23.41.

6-Amino-5-[(cyclopentylimino)methyl]-1,3-dimethyl uracil (2k): Cyclopentylamine (0.12 mL, 2.4 mmol) and LiH (11.9 mg, 3.0 mmol) were added to a suspension of **1** (493 mg, 2 mmol) in DMF (10 mL). After 3 h, the mixture was concentrated *in vacuo* and the residue was extracted using H_2O (10 mL) and CH_2Cl_2 (10 mL × 2). The combined organic layers were successively washed with H_2O (20 mL) and brine (20 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The residue was triturated with Et_2O (10 mL) and the resulting precipitate was collected on a Kiriyama funnel. mp 212 °C. ^{1}H NMR ($CDCl_3$) δ 1.60–1.79 (6H, m), 1.96–2.02 (2H, m), 3.32 (3H, s), 3.35 (3H, s), 3.84 (1H, m), 6.21 (1H, br s), 8.36 (1H, s), 11.95 (1H, br s). MS (EI) *m*/*z*: 250 (M^+). *Anal.* Calcd for $C_{12}H_{18}N_4O_2$: C, 57.58; H, 7.25; N, 22.38. Found: C, 57.39; H, 7.30; N, 22.30.

6-Amino-5-[(cyclohexylimino)methyl]-1,3-dimethyluracil (2l): Cyclohexylamine hydrochloride (298 mg, 2.2 mmol) and Et_3N (0.6 mg, 4.3 mmol) were added to a suspension of **1** (493 mg, 2 mmol) in DMF (10 mL). After 1.5 h, the mixture was poured into H_2O (10 mL). The resulting precipitate was collected on a Kiriyama funnel. mp 178–179 °C. ^{1}H NMR ($CDCl_3$) δ 1.34–1.49 (4H, m), 1.58–1.64 (2H, m), 1.76–1.79 (2H, m), 1.91–1.94 (2H, m), 3.29 (1H, m), 3.32 (3H, s), 3.34 (3H, s), 6.33 (1H, br s), 8.34 (1H, s), 12.03 (1H, br s). MS (EI) *m*/*z*: 264 (M^+). *Anal.* Calcd for $C_{13}H_{20}N_4O_2$: C, 59.07; H, 7.63; N, 21.20. Found: C, 59.13; H, 7.61; N, 21.21.

6-Amino-5-[(cyclohexylmethylimino)methyl]-1,3-dimethyluracil (2m): mp 186 °C. ^{1}H NMR ($CDCl_3$) δ 0.97 (2H, m), 1.14–1.30 (3H, m), 1.54–1.75 (6H, m), 3.29 (2H, d, *J* = 6.3 Hz), 3.32 (3H, s), 3.35 (3H, s), 6.36 (1H, br s), 8.24 (1H, s), 11.95 (1H, br s). MS (EI) *m*/*z*: 278 (M^+). *Anal.* Calcd for $C_{14}H_{22}N_4O_2$: C, 60.41; H, 7.97; N, 20.13. Found: C, 60.34; H, 7.87; N, 19.92.

General procedure for the intramolecular N–N bond formation (3a–3m). To a suspension of 6-amino-5-[(substituted)-iminomethyl]-1,3-dimethyluracil (1.94 mmol) in dry DMF (20 mL) was

dropwise added iodobenzene diacetate (2.49 g, 7.74 mmol). The mixture was stirred at 80 °C for a given time and concentrated *in vacuo*. To the residue were added H_2O (15 mL) and $CHCl_3$ (15 mL) and the layers were separated. The aqueous layer was extracted with $CHCl_3$ (15 mL × 2). The combined organic layers were successively washed with H_2O (20 mL) and brine (20 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The residue was triturated with Et_2O (10 mL) and the resulting precipitate was collected on a Kiriyama funnel and then recrystallized from MeOH.

5,7-Dimethyl-2-phenyl-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (3a)[17]: mp 288–291 °C (recrystallized from MeOH). ^{1}H NMR ($CDCl_3$) δ 3.43 (3H, s), 3.61 (3H, s), 7.39 (1H, t, *J* = 7.8 Hz), 7.51 (2H, t, *J* = 7.8 Hz), 7.72 (2H, d, *J* = 7.8 Hz), 8.43 (1H, s). MS (EI) *m*/*z*: 256 (M^+). *Anal.* Calcd for $C_{13}H_{12}N_4O_2$: C, 60.93; H, 4.72; N, 21.87. Found: C, 60.88; H, 4.86; N, 22.08.

2-(4-Fluorophenyl)-5,7-dimethyl-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (3b)[17]: mp 270–271 °C (recrystallized from EtOH). ^{1}H NMR ($CDCl_3$) δ 3.43 (3H, s), 3.60 (3H, s), 7.21 (2H, dd, *J* = 9.0, 8.5 Hz), 7.70 (2H, m), 8.36 (1H, s). MS (EI) *m*/*z*: 274 (M^+). *Anal.* Calcd for $C_{13}H_{11}FN_4O_2$: C, 56.93; H, 4.04; N, 20.43. Found: C, 56.80; H, 4.12; N, 20.21.

2-(4-Chlorophenyl)-5,7-dimethyl-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (3c)[17]: mp 290–293 °C (recrystallized from EtOH). ^{1}H NMR ($CDCl_3$) δ 3.43 (3H, s), 3.60 (3H, s), 7.48 (2H, d, *J* = 9.0 Hz), 7.67 (2H, d, *J* = 9.0 Hz), 8.40 (1H, s). MS (EI) *m*/*z*: 290 (M^+). *Anal.* Calcd for $C_{13}H_{11}ClN_4O_2$: C, 53.71; H, 3.81; N, 19.27. Found: C, 53.71; H, 3.81; N, 19.09.

2-(3-Chlorophenyl)-5,7-dimethyl-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (3d)[17]: mp 286–288 °C. ^{1}H NMR ($CDCl_3$) δ 3.43 (3H, s), 3.61 (3H, s), 7.36 (1H, d, *J* = 8.1 Hz), 7.44 (1H, t, *J* = 8.1 Hz), 7.59 (1H, d, *J* = 8.1 Hz), 7.80 (1H, s), 8.43 (1H, s). MS (EI) *m*/*z*: 290 (M^+). *Anal.* Calcd for $C_{13}H_{11}ClN_4O_2 \cdot 3/5H_2O$: C, 51.79; H, 4.08; N, 18.58. Found: C, 51.72; H, 3.84; N, 18.67.

5,7-Dimethyl-2-(3-nitrophenyl)-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (3e)[17]: mp >300 °C. ^{1}H NMR ($CDCl_3$) δ 3.44 (3H, s), 3.63 (3H, s), 7.72 (1H, t, *J* = 8.3 Hz), 8.07 (1H, dd, *J* = 8.3, 2.2 Hz), 8.24 (1H, dd, *J* = 8.3, 2.2 Hz), 8.54 (1H, s), 8.66 (1H, dd, *J* = 2.2, 2.2 Hz). MS (EI) *m*/*z*: 301 (M^+). HRMS (EI) Calcd for $C_{13}H_{11}N_5O_4$ (M^+) 301.0811. Found 301.0795.

2-(4-Methoxyphenyl)-5,7-dimethyl-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (3f)[17]: mp 260–262 °C. ^{1}H NMR ($CDCl_3$) δ 3.43 (3H, s), 3.60 (3H, s), 3.87 (3H, s), 7.01 (2H, d, *J* = 9.0 Hz), 7.61 (2H, d, *J* = 9.0 Hz), 8.31 (1H, s). MS (EI) *m*/*z*: 286 (M^+). *Anal.* Calcd for $C_{14}H_{14}N_4O_3$: C, 58.74; H, 4.93; N, 19.57. Found: C, 58.66; H, 4.97; N, 19.52.

5,7-Dimethyl-2-(1-naphthalenyl)-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (3g)[17]: mp 233–235 °C (recrystallized from MeOH). ^{1}H NMR ($CDCl_3$) δ 3.47 (3H, s), 3.62 (3H, s), 7.53–7.66 (4H, m), 7.79 (1H, d, *J* = 8.1 Hz), 7.93–8.06 (2H, m), 8.30 (1H, s). MS (EI) *m*/*z*: 306 (M^+). *Anal.* Calcd for $C_{17}H_{14}N_4O_2$: C, 66.65; H, 4.61; N, 18.29. Found: C, 66.80; H, 4.62; N, 18.32.

2,5,7-Trimethyl-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (3h)[14]: mp 206–207 °C. ^{1}H NMR ($CDCl_3$) δ 3.39 (3H, s), 3.52 (3H, s), 3.94 (3H, s), 7.87 (1H, s). MS (EI) *m*/*z*: 194 (M^+). HRMS (EI) Calcd for $C_8H_{10}N_4O_2$ (M^+) 194.0804. Found 194.0813.

2-*t*-Butyl-5,7-dimethyl-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (3i): 2i (238 mg, 1 mmol), iodobenzene diacetate (1.29 g, 4 mmol), and LiH (15.9 mg, 2 mmol) were used. The residue from the extracts was purified by column chromatography on silica gel (hexane/EtOAc, 3 : 1) to give **3i** (131 mg, 56%). mp 171–172 °C. ^{1}H NMR ($CDCl_3$) δ 1.61 (s, 9H), 3.39 (3H, s), 3.54 (3H, s), 8.02 (1H, s). MS (EI) *m*/*z*: 236 (M^+). *Anal.* Calcd for $C_{11}H_{16}N_4O_2$: C, 55.92; H, 6.83; N, 23.71. Found: C, 55.86; H, 6.78; N, 23.61.

2-*n*-Butyl-5,7-dimethyl-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (3j): 2j (477 mg, 2 mmol), iodobenzene diacetate (2.58 g, 8 mmol), and LiH (31.8 mg, 4 mmol) were used. The residue from the extracts was purified by column chromatography on silica gel (hexane/EtOAc, 3 : 1) to give **3j** (399 mg, 85%). mp 127–128 °C. ^{1}H NMR ($CDCl_3$) δ 0.96 (3H, t, *J* = 7.3 Hz), 1.34 (2H, m), 1.88 (2H, quint, *J* = 7.3 Hz), 3.39 (3H, s), 3.53 (3H, s), 4.12 (2H, t, *J* = 7.3 Hz), 7.89 (1H, s). MS (EI) *m*/*z*: 236 (M^+). *Anal.* Calcd for $C_{11}H_{16}N_4O_2$: C, 55.92; H, 6.83; N, 23.71. Found: C, 55.85; H, 6.76; N, 23.74.

2-Cyclopentyl-5,7-dimethyl-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (3k): 2k (125 mg, 0.5 mmol), iodobenzene diacetate (644 mg, 2 mmol), and LiH (8.0 mg, 1 mmol) were used. The residue from the extracts was purified by column chromatography on silica gel (hexane/EtOAc, 3 : 1) to give **3k** (89.3 mg, 72%). mp 137 °C. ^{1}H NMR ($CDCl_3$) δ 1.74 (2H, m), 1.89 (2H, m), 2.04 (2H, m), 2.18 (2H, m), 3.39 (3H, s), 3.52 (3H, s), 4.64 (1H, m), 7.93 (1H, s). MS (EI) *m*/*z*: 248 (M^+). *Anal.* Calcd for $C_{12}H_{16}N_4O_2$: C, 58.05; H, 6.50; N, 22.57. Found: C, 58.01; H, 6.46; N, 22.60.

2-Cyclohexyl-5,7-dimethyl-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (3l): 2l (132 mg, 0.5 mmol), iodobenzene diacetate (403 g, 1.25 mmol), and LiH (8.0 mg, 2 mmol) were used. The residue from the extracts was purified by column chromatography on silica gel ($CHCl_3$) to give **3l** (89.2 mg, 68%). mp 172 °C. ^{1}H NMR ($CDCl_3$) δ 1.29 (1H, m), 1.44 (2H, m), 1.65–1.78 (3H, m), 1.93 (2H, m), 2.20 (2H, m), 3.39 (3H, s), 3.53 (3H, s), 4.09 (1H, m), 7.93 (1H, s). MS (EI) *m*/*z*: 262 (M^+). *Anal.* Calcd for $C_{13}H_{18}N_4O_2$: C, 59.53; H, 6.92; N, 21.35. Found: C, 59.50; H, 7.01; N, 21.38.

2-Cyclohexylmethyl-5,7-dimethyl-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (3m): 2m (139 mg, 0.5 mmol), iodobenzene diacetate (644 mg, 2 mmol), and LiH (8.0 mg, 1 mmol) were used. The residue from the extracts was purified by column chromatography on silica gel (hexane/EtOAc, 3 : 1) to give **3m** (92.1 mg, 67%). mp 161–162 °C. ^{1}H NMR ($CDCl_3$) δ 0.97 (2H, m), 1.20–1.26 (4H, m), 1.72–1.75 (4H, m), 1.93 (1H, m), 3.39 (3H, s), 3.53 (3H, s), 3.93 (2H, d, *J* = 7.0 Hz), 7.84 (1H, s). MS (EI) *m*/*z*: 276 (M^+). *Anal.* Calcd for $C_{14}H_{20}N_4O_2$: C, 60.85; H, 7.29; N, 20.27. Found: C, 60.86; H, 7.35; N, 20.32.

General procedure for the intramolecular N–O bond formation (5a–5c). To a suspension of 5-acyl-6-amino-1,3-dimethyluracil (**4a**–**4c**) (1 mmol) in dry DMF (5 mL) were dropwise added iodobenzene diacetate (805 g, 2.5 mmol) and LiH (15.9 mg, 2 mmol). The mixture was stirred at 80 °C for a given time and concentrated *in vacuo*. To the residue were added H_2O (15 mL) and $CHCl_3$ (15 mL) and the layers were separated. The aqueous layer was extracted with $CHCl_3$ (15 mL × 2). The combined organic layers were successively washed with H_2O (20 mL) and brine (20 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The residue was then purified by column chromatography on silica gel ($CHCl_3$).

3,5,7-Trimethylisoxazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (5a)[18]: mp 201 °C. ^{1}H NMR ($CDCl_3$) δ 2.75 (3H, s), 3.37 (3H, s), 3.49 (3H, s). MS (EI) *m*/*z*: 195 (M^+). HRMS (EI) Calcd for $C_8H_9N_3O_3$ (M^+) 195.0644. Found 195.0635.

3-Ethyl-5,7-dimethylisoxazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (5b)[18]: mp 91 °C. ^{1}H NMR ($CDCl_3$) δ 1.38 (3H, t, *J* = 7.8 Hz), 3.13 (2H, q, *J* = 7.8 Hz), 3.36 (3H, s), 3.48 (3H, s). MS (EI) *m*/*z*: 209 (M^+). *Anal.* Calcd for $C_9H_{11}N_3O_3$: C, 51.67; H, 5.30; N, 20.09. Found: C, 51.55; H, 5.24; N, 19.83.

5,7-Dimethyl-3-propylisoxazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (5c)[18]: mp 43 °C. ^{1}H NMR ($CDCl_3$) δ 1.00 (3H, t, *J* = 7.6 Hz), 1.83 (2H, m), 3.07 (2H, t, *J* = 7.6 Hz), 3.34 (3H, s), 3.47 (3H, s). MS (EI) *m*/*z*: 223 (M^+). *Anal.* Calcd for $C_{10}H_{13}N_3O_3$: C, 53.81; H, 5.87; N, 18.82. Found: C, 53.89; H, 5.76; N, 18.57.

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