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SYNTHESIS, PROPERTIES, AND REDOX ABILITY OF OPTICALLY ACTIVE 3-CARBAMOYL-1,6-DIMETHYLPYRIMIDO[4,5-*c*]PYRIDAZINE-5,7(1*H*,6*H*)-DIONE AND RELATED PYRIMIDO-ANNULATED PYRIDINE ANALOGUES

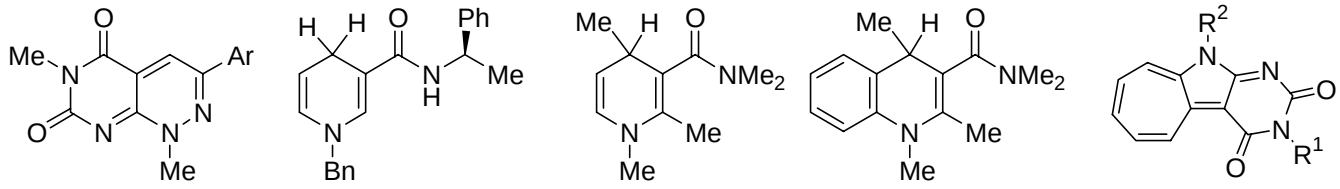
Shin-ichi Naya, Kohtaro Shibayama, and Makoto Nitta*

Department of Chemistry, School of Science and Engineering, Waseda University, Shinjuku-ku, Tokyo 169-8555, Japan

Abstract – Optically active 3-carbamoyl-1,6-dimethylpyrimido[4,5-*c*]pyridazine-5,7(1*H*,6*H*)-dione (**13a**) and related pyrimido-annulated pyridine analogues (**13b,c**) were prepared *via* the corresponding 3-ethoxycarbonyl-1,6-dimethylpyrimido[4,5-*c*]pydazine-5,7(1*H*,6*H*)-dione (**11a**) and the related compounds (**11b,c**). The properties of **11a-c**, **13a-c**, and the related 1,3,6-trimethylpyrimido[4,5-*c*]pyridazine-5,7(1*H*,6*H*)-dione (**18a**) as well as 7-phenyl- and 3,7,8-trimethyl-pyrido[2,3-*d*]pyrimidine-2,4(3*H*,8*H*)-dione (**18b,c**) having no carbamoyl or ester function were studied by the UV-VIS spectra and redox potentials. Although pyridazine derivative (**13a**) was not reduced, pyridine derivatives (**11b,c**), (**13b**), and (**18b**) were reduced by $Na_2S_2O_4$ to give dihydrogenated compounds (**20b,c**), (**21b**), and (**22b**), respectively. The photo-induced oxidation reactions of **13a,b** and **18a-c** toward some amines under aerobic conditions were studied to give the corresponding imines in more than 100% yields [based on compounds **13a,b** and **18a-c**], suggesting that the oxidation proceeds in an autorecycling process.

INTRODUCTION

1,6-Dimethylpyrimido[4,5-*c*]pyridazine-5,7(1*H*,6*H*)-dione (4-deazatoxoflavin),[1] in which the N4 of the antibiotic toxoflavin[2] is replaced by CH, has a conjugated system similar to that of flavin and 5-deazaflavin. Furthermore, one of its canonical structures can be considered to be a model of the 6-aza analogue of nicotinamide adenine dinucleotide (NAD^+). Therefore, it was expected that 4-



1 **2** **3** **4** **5**

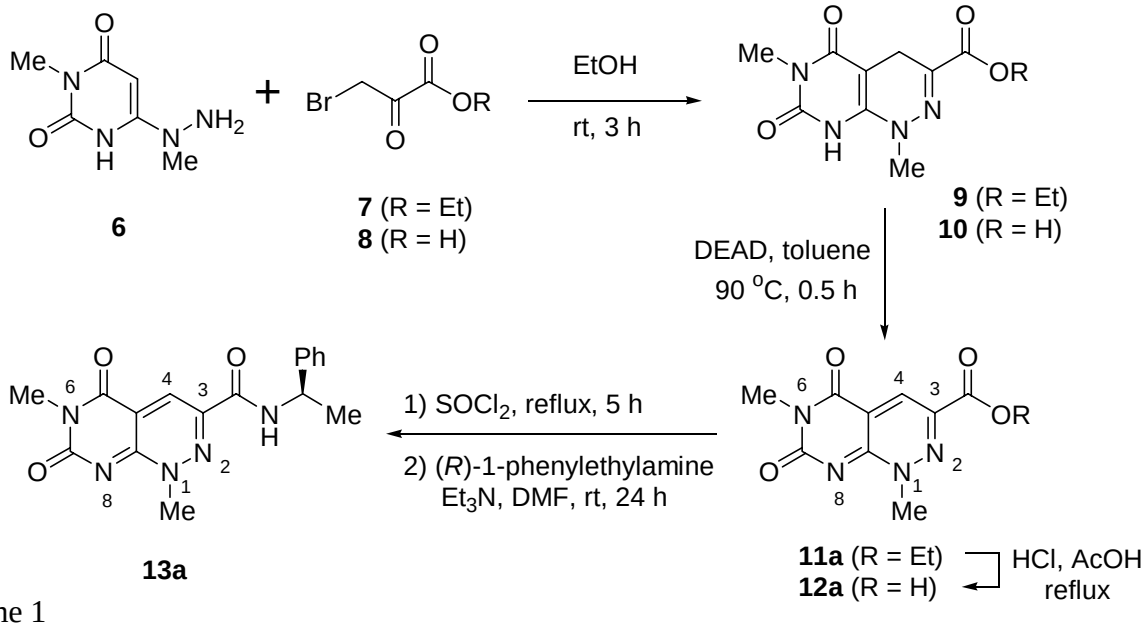
Figure 1.

deazatoxoflavin derivatives might abstract hydrogen equivalents from hydrogen donors under certain conditions. In fact, 3-aryl-4-deazatoxoflavins (**1**) have been synthesized and found to oxidize alcohols and benzylamine to the corresponding carbonyl compounds.[3] On the other hand, during several decades, efforts have been made to create model compounds mimicking the activity of the NAD^+-NADH redox couple. The introduction of an optically active N-substituent in the amide of 1-alkylated 1,4-dihydronicotinamides, e.g., **2**, can induce a modest to moderate chirality transfer toward carbonyl compounds.[4,5] Furthermore, Ohno and coworkers have improved considerably a chirality transfer by the additional introduction of methyl groups at the C2 and C4 in the NADH model, e.g., compound (**3**).[6] The new chiral center at the C4 controls the mode of hydride transfer. However, compound (**3**) has not been obtained by the $Na_2S_2O_4$ reduction of the corresponding pyridinium cation. From the view of coenzyme modeling, redox reversibility is an indispensable factor of NAD^+/NADH model systems. Thus, they have reported also the synthesis of quinolinium-type NAD^+ model compounds, which gives the corresponding dihydroquinoline (**4**) by the $Na_2S_2O_4$ reduction.[7] Accordingly, the benzo-annulation of the NAD^+ model compound is endowed with selectivity of 1,4-reduction and enhanced stability of the atropisomers. On the other hand, we have recently reported the synthesis, properties, and oxidizing ability of uracil-anuulated heteroazulenes such as 6,9-disubstituted cyclohepta[*b*]pyrimido[5,4-*d*]pyrrole-8(6*H*),10(9*H*)-diones (**5**)[8] and their related cations.[9-12] In this context, as well as to pursue our interest in enzymatic or catalytic functions, we have now studied a new synthesis, properties, and redox ability of optically active 3-carbamoyl-1,6-dimethylpyrimido[4,5-*c*]pyridazine-5,7(1*H*,6*H*)-dione (**13a**) (Scheme 1) and pyrimido-annulated pyridine analogues (**13b,c**) as well as 3- or 6-ethoxycarbonyl-substituted derivatives (**11a-c**) (Schemes 2 and 3). We report herein the results in detail.

RESULTS AND DISCUSSION

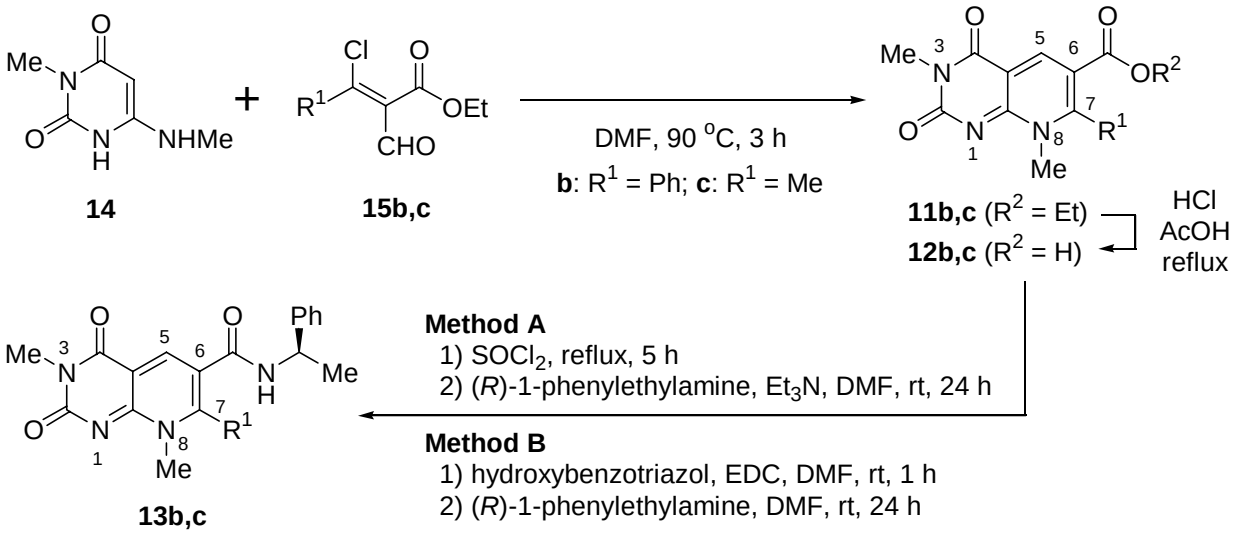
Since compound (**1**) has been synthesized by the reaction of 3-methyl-6-(1-methylhydrazino)uracil (**6**)[13] with α-bromoacetophenones,[14] the method was applied to synthesize novel optically active 3-carbamoyl-1,6-dimethylpyrimido[4,5-*c*]pyridazine-5,7(1*H*,6*H*)-dione (**13a**) (Scheme 1). The reactions of compound (**6**), which is prepared *in situ*, with **7** and **8** were carried out to give **9** and **10** in 75 and 70%

yields. Although **9** and **10** are stable under aerobic conditions, treatment with DEAD (diethyl azodicarboxylate), **9** and **10** were aromatized to give **11a** and **12a** in 84 and 25% yields, respectively. Hydrolysis of **11a** giving **12a** and subsequent treatment with $SOCl_2$ followed by reaction with (*R*)-1-phenylethylamine afforded **13a** in 38% yield. Compounds (**9**), (**10**), (**11a**), (**12a**), and (**13a**) were characterized on the basis of their ^1H and ^{13}C NMR, IR, and MS spectral data as well as elemental analyses.



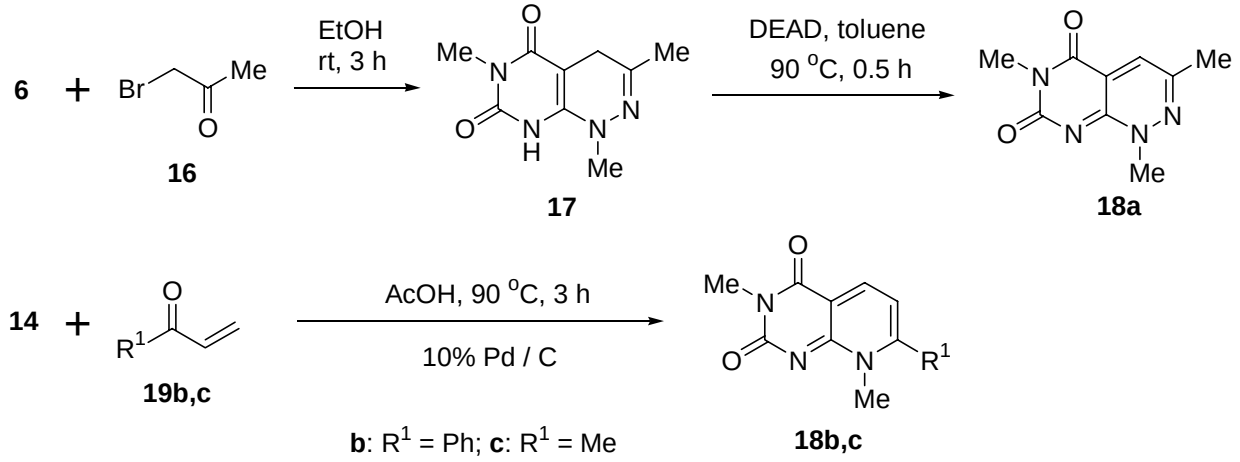
Scheme 1

Compounds (**13b,c**), in which the nitrogen atom on the C2 of **13a** is replaced by CPh and CMe, were prepared starting from the reaction of 3-methyl-6-methylaminouracil (**14**) with **15b,c** according to the modified procedure described in the literarture (Scheme 2).[15] Reactions of **14** with **15b,c**, which were obtained by the Vilsmeier reaction of ethyl benzoylacetate and ethyl acetoacetate,[16] afforded **11b,c** in 94



Scheme 2

and 45% yields, respectively. In addition, **11c** was also obtained by the reaction of ethyl acetoacetate, aqueous HCHO, and **14** in a one-flask operation in 34% yield.[17] Acid-hydrolysis of **11b,c** gave carboxylic acids (**12b,c**) in 89 and 100% yields, respectively. Upon treatment with $SOCl_2$ and subsequently with (*R*)-1-phenylethylamine, **12b** was converted to **13b** in 75% yield. On the other hand, similar treatment of **12c** afforded a complicated mixture, and thus, an activated-ester method[18] was applied for the synthesis of **13b,c**. By using hydroxybenzotriazol and EDC [*N*-ethyl-*N*′-(3-aminopropyl)carbodiimide hydrochloride], **12b,c** were converted to active esters, which were reacted with (*R*)-1-phenylethylamine to give **13b,c** albeit in low yields (**13b**,12%; **13c**, 20%). Furthermore, reference compounds (**18a-c**) were synthesized as follows:[19] the reaction of **6** with **16** giving **17** in 46% yield and subsequent dehydrogenation using DEAD gave **18a** in 49% yield (Scheme 3). On the other hand, the reactions of **14** with **19b,c** afforded **18b,c** in 33 and 76% yields, respectively. Compounds (**11b,c**)[15] and (**12b,c**),[15] and (**18c**)[19] were identified on the basis of a comparison of the physical data with those reported in the literature.[15] Compounds (**13b,c**), and (**18a,b**) are new and were characterized on the basis of the ^{1}H and ^{13}C NMR, IR, and MS spectral data as well as elemental analyses.



Scheme 3

The UV-VIS spectral data of **11a-c** and **13a-c** in MeCN are summarized in Table 1, together with those of the reference compounds (**18a-c**). The longest wavelengths absorption maxima are slightly shifted to longer wavelength in the order **11c** < **11b** < **11a.** A similar tendency is observed for **13a-c** and **18a-c**. Furthermore, differences in the wavelengths in a series of **11a-c** and those in a series of **13a-c** are 6-8 nm. Thus, the carbamoyl group on the C3 causes red-shift by 6-8 nm as compared with the ethoxycarbonyl group. Although benzylamine was added to the solution, the visible region of the spectra of **11a-c**, **13a-c**, and **18a-c** was not changed, suggesting no reaction of these compounds with benzylamine (*vide infra*) under measurement conditions of the UV-VIS spectra.

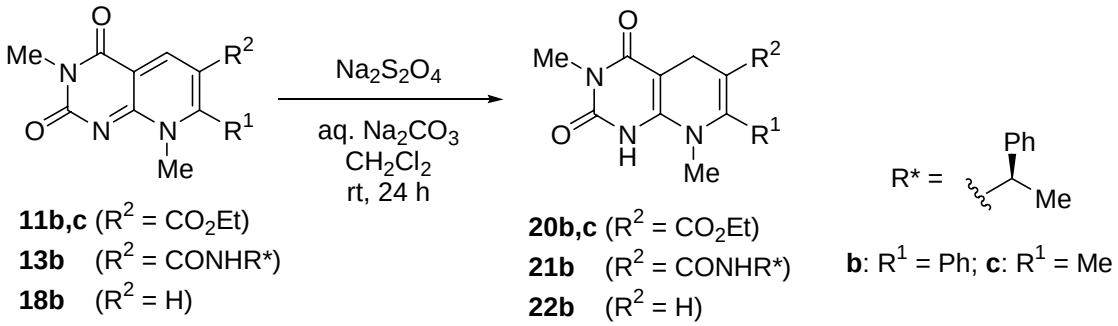
Table 1. UV-VIS spectral data and redox potentials[a] of **11a-c**, **13a-c**, and **18a-c**

	UV-VIS	Redox peak potential / V		
Compd	λ_{max} / nm (log ε / $dm^3mol^{-1}cm^{-1}$)	$E1_{red}$	$E2_{red}$	$E1_{ox}$
11a	379 (3.41), 281 (4.14)	-1.16	-1.55	---
11b	375 (3.96), 294 (4.14)	-1.67	---	+1.61
11c	370 (3.96), 297 (4.21)	-1.76	---	+1.60
13a	385 (3.46), 279 (4.26)	-1.15	-1.47	---
13b	383 (4.06), 286 (4.15)	-1.66	---	+1.46
13c	376 (3.84), 285 (3.95)	-1.80	---	+1.48
18a	384 (3.62), 263 (4.24)	-1.45	---	+1.74
18b	384 (4.11), 263 (4.23)	-1.75	---	+1.41
18c	372 (3.99), 277 (3.88)	-1.92	---	+1.15

[a] V vs $Ag/AgNO_3$ in MeCN.

The redox potentials of **11a-c**, **13a-c**, and **18a-c** were determined by cyclic voltammentry (CV) in MeCN. The redox waves were irreversible under the conditions of the CV measurements; the peak potentials are summarized in Table 1. Pyridazine derivatives (**11a**) and (**13a**) show two reduction waves ($E1_{red}$ and $E2_{red}$), while other compounds (**11b,c**), (**13b,c**), and (**18a-c**) show a reduction wave ($E1_{red}$) and an oxidation wave ($E1_{ox}$). The $E1_{red}$ is more positive in the order **11c** < **11b** < **11a**. A similar tendency is observed for **13a-c** and **18a-c**, and thus, the feature seems to be affected by the order of electron-withdrawing ability on the C2 (N, CPh, and CMe). In addition, the $E2_{red}$ of **11a** and **13a** would be ascribed to the strong electron-withdrawing effect of N2. The $E1_{red}$ of two series of **11a-c** and **13a-c** are more positive as compared with those of a series of **18a-c**, respectively, while the difference between the $E1_{red}$ in a series of **11a-c** and that in a series of **13a-c** is small, respectively. The $E1_{ox}$ values of **11b,c** are more positive as compared with those of **13b,c**, probably due to the large electron-withdrawing property of the ethoxycarbonyl group as compared with that of the carbamoyl group.

The results for the reduction of **11a-c**, **13a-c**, and **18a-c** by using $Na_2S_2O_4$ are summarized in Table 2 (Scheme 4). Reduction of **1** with $Na_2S_2O_4$ is known to give 3-aryl-4,8-dihydro-1,6-dimethyl-4-deazatoxoflavin;[14] however, pyridazine derivative (**13a**) was not reduced by $Na_2S_2O_4$ (Table 2, Run 1). Reductions of **11b**, **13b**, and **18b** having a phenyl group on the C7, however, afforded the corresponding dihydrogenated compounds (**20b**), (**21b**), and (**22b**) (Runs 2-4), respectively. Compound (**11c**), which has a methyl group on the C7, was reduced partially to give **20c** (Run 5); however, reduction of compounds (**13c**) and (**18c**) did not proceed and the starting materials were recovered (Runs 6 and 7). Since $Na_2S_2O_4$ reduction is initiated by addition of SO_2^{2-} (generated by disproportionation of $S_2O_4^{2-}$)[20] or



11b,c (R^2 = CO_2Et)
13b (R^2 = CONHR*)
18b (R^2 = H)

20b,c (R^2 = CO_2Et)
21b (R^2 = CONHR*)
22b (R^2 = H)

b: R^1 = Ph; **c**: R^1 = Me

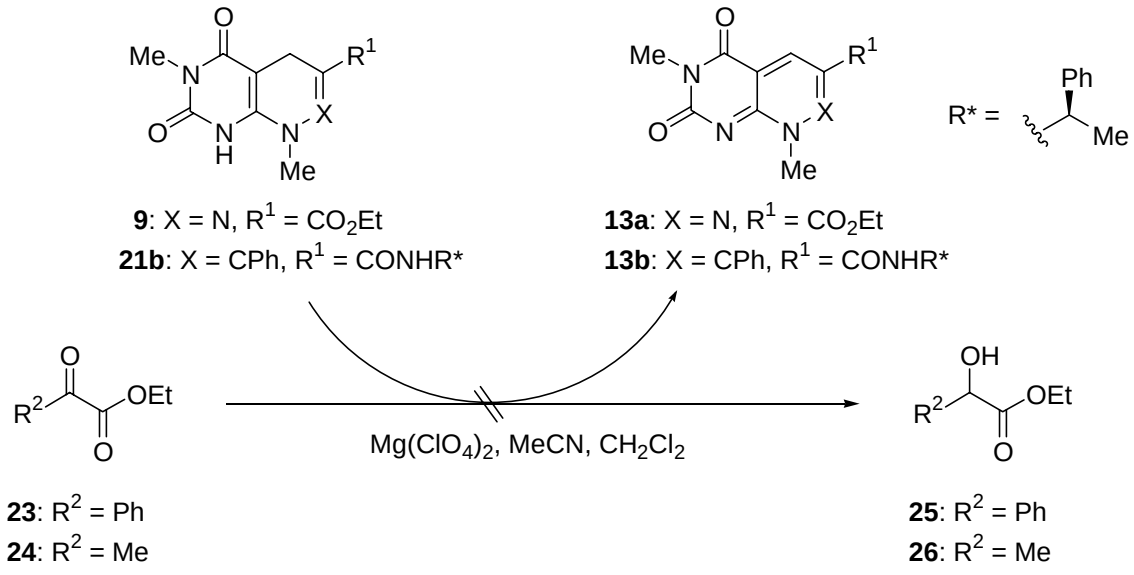
Scheme 4

by one-electron transfer to the substrate,[21,22] the reduction potential (electron-accepting ability) of the substrate is an important factor for the reactivity toward $Na_2S_2O_4$ reduction. Concerning the NADmodel compounds, the correlation of the reduction potential and the activity of $Na_2S_2O_4$ reduction has been reported previously, and compounds having less negative reduction potentials (–1.43 V to –1.62 V) are reduced by $Na_2S_2O_4$, which could not reduce compounds having more negative reduction potentials (–1.84 V to –1.94 V).[7] A similar feature is observed in **11b,c**, **13b,c**, and **18b,c**. Pyridine derivatives (**11b,c**), (**13b**), and (**18b**) having less negative reduction potentials (–1.67 V to –1.76 V) are reduced by $Na_2S_2O_4$, while **13c** and **18c** having more negative reduction potentials (–1.80 V and –1.92 V) are not reduced.

Table 2. Results for reduction of **11b,c**, **13a-c**, and **18b,c**

Run	Compd	Product (Yield)
1	**13a**	**13a** (100%)
2	**11b**	**20b** (100%)
3	**13b**	**21b** (100%)
4	**18b**	**22b** (60%), **18b** (40%)[a]
5	**11c**	**20c** (60%), **11c** (40%)[a]
6	**13c**	**13c** (100%)
7	**18c**	**18c** (100%)

[a] Product ratio was determined by ^{1}H NMR spectroscopy.



9: X = N, R^1 = CO_2Et
21b: X = CPh, R^1 = CONHR*

13a: X = N, R^1 = CO_2Et
13b: X = CPh, R^1 = CONHR*

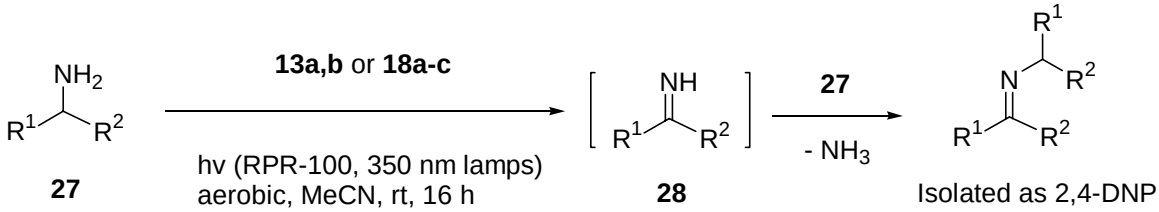
23: R^2 = Ph
24: R^2 = Me

25: R^2 = Ph
26: R^2 = Me

Scheme 5

Dihydrogenated compounds (**9**) and (**21b**) were used for reduction of ethyl benzoylformate (**23**) and ethyl acetoformate (**24**) (Scheme 5). However, reduction did not proceed and **23** and **24** were recovered quantitatively. Compound (**9**) is stable and was recovered quantitatively; however, **13b** was obtained instead of **21b** quantitatively probably due to the easy oxidation of **21b** by stray oxygen.

We have previously reported that compounds (**5**) undergo autorecycling oxidation toward some amines under photo-irradiation.[8] In this context and in a search for the oxidizing ability of pyrido[2,3-*d*]pyrimidine-2,4(3*H*,8*H*)-diones and related compounds, we examined the oxidation of some amines by using **13a,b** and **18a-c**. Although under thermal and aerobic conditions, these compounds did not oxidize amines, under photo-irradiation and aerobic conditions (RPR-100, 350 nm lamps), we found that these compounds have oxidizing ability toward some benzylic amines to give the corresponding imines. Imine (**28**) is produced at first; however, it reacts with another amine to result in the formation of substituted imine (Scheme 6).[3] The results are summarized in Table 3 (Runs 1-22). Direct



Scheme 6

Table 3. Autorecycling oxidation of some amines by using **13a,b** and **18a-c** under photo-irradiation [a]

Run	Compd	Amine	Yield [b,c] (%)	Run	Compd	Amine	Yield [b,c] (%)
1	**13a**	$PhCH_2NH_2$	9650	12	**13a**	$4\text{-}MeC_6H_4CH_2NH_2$	1380
2	**13b**	$PhCH_2NH_2$	3762	13	**13a**	$4\text{-}ClC_6H_4CH_2NH_2$	10215
3	**18a**	$PhCH_2NH_2$	4587	14	**13a**	$4\text{-}PyCH_2NH_2$	369
4	**18b**	$PhCH_2NH_2$	2300	15	**13b**	$4\text{-}MeOC_6H_4CH_2NH_2$	4785
5	**18c**	$PhCH_2NH_2$	2119	16	**13b**	$4\text{-}MeC_6H_4CH_2NH_2$	2313
6	**13a**	$PhCH(Me)NH_2$	6727	17	**13b**	$4\text{-}ClC_6H_4CH_2NH_2$	8087
7	**13b**	$PhCH(Me)NH_2$	2987	18	**13b**	$4\text{-}PyCH_2NH_2$	5686
8	**18a**	$PhCH(Me)NH_2$	9747	19	**13a**	cyclohexyamine	0 [d]
9	**18b**	$PhCH(Me)NH_2$	5700	20	**13b**	cyclohexyamine	0 [d]
10	**18c**	$PhCH(Me)NH_2$	3133	21	**13a**	butylamine	0 [d]
11	**13a**	$4\text{-}MeOC_6H_4CH_2NH_2$	3538	22	**13b**	butylamine	158

[a] MeCN solution was irradiated by RPR-100, 350 nm lamps under aerobic conditions. [b] Isolated by converting to the corresponding 2,4-dinitrophenylhydrazone. [c] Based on **13a,b** and **18a-c** used; the yield is calculated by subtraction of the "blank" yield from the total yield of imines in the presence of **13a,b** and **18a-c**. [d] The "blank" yield was higher than the yield in the presence of **13a,b**.

irradiation of the amines in the absence of a catalyst (named "blank") gives the imines in low to modest yields. Thus, the yields are calculated by subtraction of the "blank" yield from the yields in the presence of **13a,b** and **18a-c**. More than 100% yields are obtained [based on compounds **13a,b** and **18a-c**] (Table 3), and thus, autorecycling oxidation clearly proceeds; however, cyclohexylamine and butylamine were not oxidized effectively (Table 3, Runs 19-22). In the oxidation of benzylamine by using **13a,b** and **18a-c**, the yields of the imines became higher in the order **13b** < **13a** and **18c** < **18b** < **18a** (Table 3, Runs 1-5). This fact is probably due to the more positive $E1_{red}$ values in the order **13b** < **13a** and **18c** < **18b** < **18a**. [The reduction potentials of **13a,b** and **18a-c** in the ground state would be correlated with their LUMOs, and thus, the LUMOs of these compounds would be lower in the order **13b** > **13a** and **18c** > **18b** > **18a**. In the excited state of these compounds, the electron-accepting orbital would be the singly occupied HOMOs. The UV-VIS spectra of these compounds are similar, and the energy level of HOMOs of the compounds is expected to be lower in the order **13b** > **13a** and **18c** > **18b** > **18a**, and thus, the autorecycling oxidation of amines seems to be more efficient in the order order **13b** < **13a** and **18c** < **18b** < **18a**.] A similar trend was observed in the oxidation of 1-phenylethylamine (Table 3, Runs 6-10). However, no clear correlation between the oxidation yields by using **13a,b** and those by using **18a-c** was observed. In a search for the substituent effect on the benzylamine oxidation, the oxidation reactions of 4-substituted benzylamines and 4-picolylamine were carried out by using **13a**,**b** under aerobic and photo-irradiation conditions (Table 3, Runs 11-18); however, no clear correlation was observed. Attempted detection of the dihydrogenated compounds of **13a,b** and **18a-c**, all of which are expected from the amine oxidation reaction,[3] has so far not been successful. Thus, further investigations will be required to clarify the mechanistic aspect of the present autorecycling oxidation reaction.

In summary, a convenient preparation of novel optically active 3-carbamoyl-1,6-dimethylpyrimido[4,5-*c*]pyridazine-5,7(1*H*,6*H*)-dione (**13a**) and related pyrimido-annulated pyridine (**13b,c**) and a series of ethoxycarbonyl-substituted analogues (**11a-c**) as well as a series of **18a-c** was accomplished. The properties of **11a-c**, **13a-c**, and **18a-c** were studied by the UV-VIS spectra and redox potentials. The photo-induced oxidation reactions of **13a,b** and **18a-c** toward some amines under aerobic conditions were carried out to give the corresponding imines in more than 100% yield [based on compounds (**13a,b**) and (**18a-c**)], suggesting that the oxidation proceeds in an autorecycling process.

EXPERIMENTAL

IR spectra were recorded on a HORIBA FT-710 spectrophotometer. MS spectra and HRMS spectra were run on JMS-AUTOMASS 150 (EI), ThermoQuest LCQ (ESI), KRATOS AXIMA-CFR (MALDI), and JMS-SX102A spectrometers, respectively. Unless otherwise specified, ^{1}H NMR spectra and ^{13}C

NMR spectra were recorded on JNM-AL 400, JNM-lambda 500, and AVANCE 600 spectrometers using $CDCl_3$ as the solvent, and the chemical shifts are given relative to internal $SiMe_4$ standard: *J*-values are given in Hz. Mps were recorded on a Yamato MP-21 apparatus and were uncorrected. The 3-methyl-6-methylaminouracil (**14**)[23] were prepared as described previously.

Preparation of 9 and 10. A solution of 6-chloro-3-methyluracil (1.60 g, 10 mmol) and methylhydrazine (1.01 g, 22 mmol) in EtOH (10 mL) was heated under reflux for 1 h. After the reaction was completed, the reaction mixture was concentrated *in vacuo* and the resulting residue was washed with Et_2O to give **6**. To the residue was added a solution of **7** or **8** (10 mmol) in EtOH (10 mL), and the mixture was stirred at rt for 3 h. The precipitates were collected by filtration, washed with Et_2O to give **9** (2.00 g, 75%) or **10** (1.67 g, 70%).

For 3-ethoxycarbonyl-4,8-dihydro-1,6-dimethylpyrimido[4,5-*c*]pyridazine-5,7(1*H*,6*H*)-dione (**9**): yellow needles; mp 210-212 ºC (from EtOH-CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.36 (3H, t, J = 7.1 Hz, $CH_2C\underline{H}_3$), 3.30 (3H, s, N6Me), 3.46 (2H, s, H-4), 3.61 (3H, s, N1Me), 4.34 (2H, q, J = 7.1 Hz, $C\underline{H}_2CH_3$), 10.64 (1H, s, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.2, 20.7, 27.3, 39.5, 62.1, 82.2, 139.4, 142.7, 152.0, 161.8, 162.9; IR ($CHCl_3$) 3447, 1710, 1653, 1635 cm^{-1}; MS (ESI) (m/z) 267 (M^++H). Anal. Calcd for $C_{11}H_{14}N_4O_4\cdot 1/2H_2O$: C, 48.00; H, 5.49; N, 20.35. Found: C, 48.12; H, 5.29; N, 20.51.

For 3-carboxyl-4,8-dihydro-1,6-dimethylpyrimido[4,5-*c*]pyridazine-5,7(1*H*,6*H*)-dione (**10**): yellow powder; mp 229-230 ºC (from H_2O); ^{1}H NMR (600 MHz, DMSO-d_6) δ 3.11 (3H, s, N6Me), 3.12 (2H, s, H-4), 3.43 (3H, s, N1Me), 11.06 (1H, s, NH); ^{13}C NMR (150 MHz, DMSO-d_6) δ 20.1, 26.5, 39.3, 80.0, 138.7, 143.3, 150.3, 161.6, 164.3; IR (KBr) 3442, 1700, 1653, 1600 cm^{-1}; MS (ESI) (m/z) 239 (M^++H). Anal. Calcd for $C_9H_{10}N_4O_4\cdot H_2O$: C, 42.19; H, 4.72; N, 21.87. Found: C, 42.25; H, 4.77; N, 22.08.

Preparation of 11a and 12a. To a solution of DEAD (diethyl azodicarboxylate) (582 mg, 3.3 mmol) in toluene (5 mL) was added **9** (445 mg, 1.67 mmol) or **10** (397 mg, 1.67 mmol), and the mixture was heated at 90 ºC for 30 min. After the reaction was completed, the mixture was cooled to rt and diluted with Et_2O. The precipitates were collected by filtration to give **11a** (370 mg, 84%) or **12a** (98 mg, 25%), respectively.

For 3-ethoxycarbonyl-1,6-dimethylpyrimido[4,5-*c*]pyridazine-5,7(1*H*,6*H*)-dione (**11a**): yellow needles; mp 175-178 ºC (from EtOH-Et_2O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.45 (3H, t, J = 7.1 Hz, $CH_2C\underline{H}_3$), 3.46 (3H, s, N6Me), 4.28 (3H, s, N1Me), 4.51 (2H, q, J = 7.1 Hz, $C\underline{H}_2CH_3$), 8.75 (1H, s, H-4); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.2, 28.5, 44.5, 63.2, 122.6, 130.7, 139.4, 155.7, 156.1, 159.9, 160.7; IR ($CHCl_3$) 1664,

1628, 1602 cm^{-1}; MS (EI) (m/z) 264 (M^+, 100 %). Anal. Calcd for $C_{11}H_{12}N_4O_4$: C, 50.00; H, 4.58; N, 21.20. Found: C, 49.62; H, 4.66; N, 21.10.

For 3-carboxyl-1,6-dimethylpyrimido[4,5-*c*]pyridazine-5,7(1*H*,6*H*)-dione (**12a**): yellow powder; mp 244-245 ºC (from H_2O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.24 (3H, s, N6Me), 4.01 (3H, s, N1Me), 8.40 (1H, s, H-4); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.7, 43.6, 122.4, 129.4, 139.5, 155.0, 155.9, 160.0, 162.2; IR (KBr) 3502, 3056, 1714, 1663, 1608 cm^{-1}; MS (EI) (m/z) 236 (M^+, 100%). Anal. Calcd for $C_9H_8N_4O_4 \cdot 2H_2O$: C, 39.71; H, 4.44; N, 20.58. Found: C, 39.66; H, 4.45; N, 20.46.

Preparation of 13a. A solution of **11a** (264 mg, 1 mmol) in AcOH (10 mL) and 36% HCl (1 mL) was heated under reflux for 5 h. The reaction mixture was concentrated *in vacuo* to give **12a**, which was dissolved in $SOCl_2$ (5 mL, 64 mmol) and heated under reflux for 5 h. After the solvent was evaporated, DMF (3 mL), Et_3N (505 mg, 5 mmol), and (*R*)-1-phenylethylamine (182 mg, 1.5 mmol) were added to the mixture. The solution was stirred at rt for 24 h, and then the reaction mixture was poured into 7% aq. $NaHCO_3$ solution. The mixture was extracted with CH_2Cl_2, and the extract was dried over Na_2SO_4, and concentrated *in vacuo*. The resulting residue was purified through column chromatography on Al_2O_3 by using AcOEt as the eluent to give **13a** (130 mg, 38%).

For 1,6-dimethyl-3-(*N*-(*R*)-phenylethylcarbamoyl)pyrimido[4,5-*c*]pyridazine-5,7(1*H*,6*H*)-dione (**13a**): yellow powder; mp 79-82 ºC (from AcOEt-hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.65 (3H, d, J = 7.0 Hz, CH(Ph)C<u>H</u>$_3$), 3.43 (3H, s, N6Me), 4.20 (3H, s, N1Me), 5.32 (1H, dq, J = 7.6, 7.0 Hz, C<u>H</u>(Ph)CH_3), 7.29-7.38 (6H, m, Ph, NH), 8.89 (1H, s, H-4); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.5, 28.4, 44.0, 49.4, 123.2, 126.3, 127.9, 128.9, 129.8, 141.4, 142.2, 155.8, 155.9, 158.7, 159.8; IR ($CHCl_3$) 1652, 1638 cm^{-1}; MS (EI) (m/z) 339 (M^+, 12%), 120 (100); HRMS (FAB) calcd for $C_{17}H_{18}N_5O_3$: 340.1410 (M+H). Found: 340.1420 (M^++H). Anal. Calcd for $C_{17}H_{18}N_5O_3$: C, 60.17; H, 5.05; N, 20.64. Found: C, 58.96; H, 5.24; N, 19.63.

Preparation of 11b,c. A solution of **14** (1.55 g, 10 mmol) and **15b,c** (11 mmol) in DMF (1 mL) was heated at 90 ºC for 3 h. After the solvent removal *in vacuo*, the resulting residue was purified through column chromatography on SiO_2 by using AcOEt as the eluent to give **11b,c** (**11b**: 3.19 g, 94%, **11c**: 1.25 g, 45%). Physical data of **11b,c** were identical with those in the literature.[15]

One-flask operation of the prepartion of 11c. A solution of **14** (155 mg, 1 mmol), 35% aq. HCHO (86 mg, 1 mmol), and ethyl acetylacetate (130 mg, 1 mmol) in DMF (5 mL) was heated at 90 ºC for 16 h.

After the solvent was removed *in vacuo*, the residue was poured into H_2O. The mixture was extracted with CH_2Cl_2, and the extract was dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified through column chromatography on SiO_2 by using AcOEt as the eluent to give **11c** (94 mg, 34%).

Acid-hydrolysis of 11b,c. A solution of **11b,c** (1 mmol) in AcOH (10 mL) and 36% HCl (1 mL) was heated under reflux for 5 h. The reaction mixture was concentrated *in vacuo* to give **12b,c** (**12b**: 277 mg, 89%, **12c**: 249 mg, 100%).[15]

Preparation of 13b. A solution of **12b** (1.24 g, 4 mmol) in $SOCl_2$ (16 mL, 205 mmol) was heated under reflux for 5 h. After the solvent was evaporated, DMF (10 mL), Et_3N (3.03 g, 30 mmol) and (*R*)-1-phenylethylamine (726 mg, 6 mmol) were added to the mixture. The solution was stirred at rt for 5 h, and then the reaction mixture was poured into 7% aq. $NaHCO_3$ solution. The mixture was extracted with CH_2Cl_2, and the extract was dried over Na_2SO_4 and concentrated *in vacuo* to give **13b** (1.24 g, 75%).

For 3,8-dimethyl-6-(*N*-(*R*)-phenylethylcarbamoyl)-7-phenylpyrido[2,3-*d*]pyrimidine-2,4(3*H*,8*H*)-dione (**13b**): yellow needles; mp 270-272 ºC (from EtOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.20 (3H, d, J = 7.0 Hz, CH(Ph)C<u>H</u>$_3$), 3.18 (3H, s, N3Me), 3.63 (3H, s, N8Me), 4.92 (1H, dq, J = 7.5, 7.0 Hz, C<u>H</u>(Ph)CH$_3$), 7.08-7.27 (6H, m, Ph, NH), 7.50-7.61 (5H, m, Ph), 8.52 (1H, s, H-5); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.2, 28.0, 37.7, 49.5, 113.6, 123.6, 126.2, 127.4, 128.4, 128.5, 128.6, 129.5, 129.5, 131.1, 131.5, 140.1, 142.2, 154.6, 156.5, 157.1, 160.9, 163.3; IR ($CHCl_3$) 3021, 1648, 1618, 1507, 1495 cm^{-1}; MS (EI) (m/z) 414 (M^+, 94%), 294 (100). Anal. Calcd for $C_{24}H_{22}N_4O_3$: C, 69.55; H, 5.35; N, 13.52. Found: C, 69.31; H, 5.12; N, 13.43.

Preparation of 13b,c by activated-ester method. To a stirred solution of **12b,c** (1.0 mmol) in DMF (2 mL) was added hydroxybenozotriazol (150 mg, 1.1 mmol) and EDC (N-ethyl-N'-(3-amino)propylcarbodiimide hydrochloride) (210 mg, 1.1 mmol). The mixture was stirred at rt for 1 h, and the resulting mixture was poured into ice water. The precipitates were collected by filtration and washed with cold water to give an activated ester, which was used for the next step without further purification.

To a solution of the activated ester in DMF (1 mL) was added (*R*)-1-phenylethylamine (242 mg, 2 mmol), and the mixture was stirred at rt for 24 h. The reaction mixture was poured into H_2O and extracted

with CH_2Cl_2. The extract was dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified through column chromatography on SiO_2 by using acetone as the eluent to give **13b,c** (**13b**: 50 mg, 12%, **13c**: 69 mg, 20%).

For 3,7,8-trimethyl-6-(*N*-(*R*)-phenylethylcarbamoyl)pyrido[2,3-*d*]pyrimidine-2,4(3*H*,8*H*)-dione (**13c**): colorless powder; mp 157-158 ºC (from EtOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.65 (3H, d, J = 7.0 Hz, CH(Ph)C<u>H</u>$_3$), 2.68 (3H, s, 7-Me), 3.18 (3H, s, N3Me), 3.86 (3H, s, N8Me), 5.26 (1H, dq, J = 7.8, 7.0 Hz, C<u>H</u>(Ph)CH$_3$), 7.26-7.46 (5H, m, Ph), 7.89 (1H, d, J = 7.8 Hz, NH), 8.26 (1H, s, H-5); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.3, 21.9, 28.1, 34.8, 50.0, 111.6, 122.5, 126.3, 127.6, 128.8, 139.1, 142.9, 155.7, 156.2, 156.9, 161.4, 164.5; IR ($CHCl_3$) 1709, 1635, 1619 cm^{-1}; MS (EI) (m/z) 352 (M^+, 21%), 120 (100); HRMS (FAB) calcd for $C_{19}H_{20}N_4O_3$: 353.1614 (M+H). Found: 353.1599 (M^++H).

Preparation of 17. A solution of 6-chloro-3-methyluracil (1.60 g, 10 mmol) and methylhydrazine (1.01 g, 22 mmol) in EtOH (10 mL) was heated under reflux for 1 h to give **6**. After the reaction was completed, the reaction mixture was concentrated *in vacuo* and the resulting residue was washed with Et_2O. To the residue was added a solution of **16** (10 mmol) in EtOH (10 mL), and the mixture was stirred at rt for 3 h. The precipitates were collected by filtration, washed with Et_2O to give **17** (957 mg, 46%).

For 4,8-dihydro-1,3,6-trimethylpyrimido[4,5-*c*]pyridazine-5,7(1*H*,6*H*)-dione (**17**): colorless powder; mp 204-205 ºC (from EtOH); ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.88 (3H, s, 3-Me), 2.98 (2H, s, CH_2), 3.09 (3H, s, N6Me), 3.28 (3H, s, N1Me), 10.79 (1H, s, NH); ^{13}C NMR (150 MHz, DMSO-d_6) δ 22.5, 24.6, 26.4, 38.7, 76.8, 144.2, 149.2, 150.4, 161.4; IR (KBr) 3405, 1708, 1639 cm^{-1}; MS (EI) (m/z) 208 (M^+, 100%). Anal. Calcd for $C_9H_{12}N_4O_2$: C, 51.92; H, 5.81; N, 26.91. Found: C, 51.70; H, 5.93; N, 26.75.

Preparation of 18a. To a solution of diethylazodicarboxylate (DEAD) (582 mg, 3.3 mmol) in toluene (5 mL) was added **17** (347 mg, 1.67 mmol), and the mixture was heated at 90 ºC for 30 min. After the reaction was completed, the mixture was cooled to rt and diluted with Et_2O. The precipitates were collected by filtration to give **18a** (169 mg, 49%).

For 1,3,6-trimethylpyrimido[4,5-*c*]pyridazine-5,7(1*H*,6*H*)-dione (**18a**): yellow plates; mp 234-235 ºC (from EtOH); ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.57 (3H, s, 3-Me), 3.44 (3H, s, N6Me), 4.16 (3H, s, N1Me), 8.10 (1H, s, H-4); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.1, 28.4, 43. 6, 122.7, 132.0, 148.5, 154.5, 156.0,

160.4; IR ($CHCl_3$) 1652, 1638 cm^{-1}; MS (MALDI) (m/z) 207 (M^++H). Anal. Calcd for $C_9H_{10}N_4O_2$: C, 52.42; H, 4.89; N, 27.17. Found: C, 52.27; H, 4.67; N, 27.22.

Preparation of 18b. A mixture of **14** (1.7 g, 11 mmol), **19b** (1.74 g, 13.2 mmol), and 10% Pd/C (55 mg) in AcOH (10 mL) was heated at 90 ºC for 3 h. After the reaction was completed, the solvent was removed *in vacuo*, and the resulting residue was purified through column chromatography on SiO_2 by using acetone as the eluent to give **18b** (0.99 g, 33%).

For 3,8-dimethyl-7-phenylpyrimido[2,3-*d*]pyrimidine-2,4(3*H*,8*H*)-dione (**18b**): yellow needles; mp 249-250 ºC (from EtOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.48 (3H, s, N3Me), 3.84 (3H, s, N8Me), 6.77 (1H, d, J = 7.5 Hz, H-6), 7.41-7.45 (2H, m, Ph), 7.56-7.62 (3H, m, Ph), 8.55 (1H, d, J = 7.5 Hz, H-5); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.1, 38.1, 113.4, 114.4, 128.2, 129.4, 130.9, 133.8, 140.9, 156.9, 157.1, 157.2, 162.2; IR ($CHCl_3$) 1635, 1621 cm^{-1}; MS (EI) (m/z) 267 (M^+, 100%). Anal. Calcd for $C_{15}H_{13}N_3O_2$: C, 67.41; H, 4.90; N, 15.72. Found: C, 67.10; H, 4.93; N, 15.66.

Preparation of 18c. A mixture of **14** (775 mg, 5 mmol), **19c** (420 mg, 6 mmol), and 10% Pd/C (25 mg) in DMF (5 mL) was heated at 90 ºC for 3 h. After the reaction was completed, the solvent was removed *in vacuo*, and the resulting residue was purified through column chromatography on SiO_2 by using acetone as eluent to give **18c** (0.78 g, 76%).

For 3,7,8-trimethylpyrimido[2,3-*d*]pyrimidine-2,4(3*H*,8*H*)-dione (**18c**): yellow needles; mp 238-239 ºC (from AcOEt); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.65 (3H, s, 7-Me), 3.43 (3H, s, N3Me), 3.99 (3H, s, N8Me), 6.71 (1H, d, J = 7.6 Hz, H-6), 8.41 (2H, d, J = 7.6 Hz, H-5); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.2, 28.0, 34.6, 112.3, 113.5, 141.0, 154.5, 157.1, 157.2, 162.2; IR ($CHCl_3$) 3022, 1689, 1635 cm^{-1}; MS (MALDI) (m/z) 206 (M^++H). Anal. Calcd for $C_{10}H_{11}N_3O_2$: C, 58.53; H, 5.40; N, 20.48. Found: C, 58.33; H, 5.30; N, 20.47.

Cyclic Voltammetry of 11a-c, 13a-c, and 18a-c. The reduction potential was determined by means of CV-27 voltammetry controller (BAS Co). A three-electrode cell was used, consisting of Pt working and counter electrodes and a reference $Ag/AgNO_3$ electrode. Nitrogen was bubbled through an MeCN solution (4 mL) of **11a-c, 13a-c**, and **18a-c** (0.5 mmol dm^{-3}) and Bu_4NClO_4 (0.1 mol dm^{-3}) to deaerate it. The measurements were made at a scan rate of 0.1 V s^{-1} and the voltammograms were recorded on a WX-1000-UM-019 (Graphtec Co) X-Y recorder. Immediately after the measurements, ferrocene (0.1 mmol) ($E_{1/2}$ = +0.083) was added as the internal standard, and the observed peak potential was corrected

with reference to this standard. Compounds (**11a-c**), (**13a-c**), and (**18a-c**) exhibited irreversible redox waves, and they are summarized in Table 1.

$Na_2S_2O_4$ reduction of 11b,c, 13a-c, and 18b,c. To a solution of **11b,c, 13a-c**, and **18b,c** (0.05 mmol) in CH_2Cl_2 (1 mL) and 0.5 M Na_2CO_3 (3 mL) was added $Na_2S_2O_4$ (52 mg, 0.3 mmol), and the mixture was stirred at rt for 24 h. The resulting mixture was extracted with CH_2Cl_2, and the extract was dried over Na_2SO_4 and concentrated *in vacuo* to give the product. The results are summarized in Table 2.

For 6-ethoxycarbonyl-1,5-dihydro-3,8-dimethyl-7-phenylpyrido[2,3-*d*]pyrimidine-2,4(3*H*,8*H*)-dione (**20b**): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.92 (3H, t, J = 7.1 Hz, $CH_2C\underline{H}_3$), 2.90 (3H, s, N3Me), 3.25 (3H, s, N8Me), 3.50 (2H, s, CH_2), 3.88 (2H, q, J = 7.1 Hz, $C\underline{H}_2CH_3$), 7.20-7.60 (6H, m, Ph, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.2, 22.0, 27.1, 34.4, 60.0, 87.5, 106.3, 128.2, 128.6, 128.7, 128.8, 129.0, 135.1, 145.7, 150.3, 152.4, 162.3, 166.7; IR ($CHCl_3$) 3441, 1671, 1635 cm^{-1}; MS (ESI) (m/z) 342 (M^++H); HRMS (FAB) calcd for $C_{18}H_{20}N_3O_4$: 342.1454 (M+H). Found: 342.1443 (M^++H).

For 1,5-dihydro-3,8-dimethyl-7-phenyl-6-(*N*-(*R*)-phenylethylcarbamoyl)pyrido[2,3-*d*]pyrimidine-2,4(3*H*,8*H*)-dione (**21b**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.03 (3H, d, J = 6.8 Hz, CH(Ph)C$\underline{H}_3$), 2.89 (3H, s, N3Me), 3.23 (3H, s, N8Me), 3.42 (1H, d, J = 18.4 Hz, CH_2), 3.48 (1H, d, J = 18.4 Hz, CH_2), 4.82 (1H, dq, 7.6, 6.8 Hz, NH C$\underline{H}$(Ph)CH_3), 6.87-7.54 (11H, m, Ph, NH); ^{13}C NMR (150 MHz, $CDCl_3$) δ 20.9, 23.0, 27.1, 34.7, 48.5, 86.8, 112.7, 126.0, 127.2, 127.5, 128.2, 128.5, 128.6, 129.3, 129.4, 129.7, 129.7, 133.7, 140.9, 142.5, 146.3, 152.3, 162.3, 166.9; IR ($CHCl_3$) 3440, 1699, 1671 cm^{-1}; MS (ESI) (m/z) 417 (M^++H); HRMS (FAB) calcd for $C_{24}H_{25}N_4O_3$: 417.1927 (M+H). Found: 417.1896 (M^++H).

For 1,5-dihydro-3,8-dimethyl-7-phenylpyrido[2,3-*d*]pyrimidine-2,4(3*H*,8*H*)-dione (**22b**): ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.01 (3H, s, N3Me), 3.29 (2H, d, J = 4.0 Hz, CH_2), 3.30 (3H, s, N8Me), 5.05 (1H, t, J = 4.0 Hz, H-6) 7.26-7.96 (5H, m, Ph), 10.31 (1H, s, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.5, 27.0, 53.4, 86.5, 107.4, 127.9, 128.5, 128.6, 128.6, 133.5, 136.3, 141.3, 147.9, 152.4, 162.9; IR ($CHCl_3$) 3388, 1709, 1690 cm^{-1}; MS (ESI) (m/z) 270 (M^++H); HRMS (FAB) calcd for $C_{15}H_{16}N_3O_2$: 270.1243 (M+H). Found: 270.1259 (M^++H).

For 6-ethoxycarbonyl-1,5-dihydro-3,6,8-trimethylpyrido[2,3-*d*]pyrimidine-2,4(3*H*,8*H*)-dione (**20c**): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.30 (3H, t, J = 7.1 Hz, $CH_2C\underline{H}_3$), 2.42 (3H, s, 7-Me), 3.28 (3H, s, N3Me), 3.29 (3H, s, N8Me), 3.34 (2H, s, CH_2), 4.19 (2H, q, J = 7.1 Hz, $C\underline{H}_2CH_3$), 10.50 (1H, s, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.3, 16.3, 21.5, 27.1, 32.6, 60.3, 87.4, 105.2, 145.5, 147.3, 152.5, 162.3, 167.5; MS

(ESI) (m/z) 280 (M^++H); HRMS (FAB) calcd for $C_{13}H_{17}N_3O_4$: 280.1297 (M+H). Found: 280.1281 (M^++H).

Attempted reduction of 23 and 24 by 9 and 21b. To a solution of **9** or **21b** (0.1 mmol) and $Mg(ClO_4)_2$ (22 mg, 0.1 mmol) in CH_2Cl_2 (5 mL) and MeCN (5 mL) was added **23** or **24** (0.1 mmol), and the mixture was stirred under the conditions indicated in Table 3. The resulting mixture was extracted with CH_2Cl_2, and the extract was dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified through column chromatography on SiO_2 by using AcOEt as the eluent to give the starting materials **23** or **24** (0.1 mmol, 100%) as well as **9** (27 mg, 100%) or **13b** (41 mg, 100%).

General procedure for the autorecycling oxidation of amines by 13a,b and 18a-c. An MeCN (16 mL) solution of compounds **13a,b** and **18a-c** (0.005 mmol) and amines (2.5 mmol, 500 eq.) in a Pyrex tube was irradiated by RPR-100, 350 nm lamps under aerobic conditions for 16 h. The reaction mixture was concentrated *in vacuo* and diluted with Et_2O and filtered. The ^{1}H NMR spectra of the filtrates revealed the formation of the corresponding imines. The filtrate was treated with a saturated solution of 2,4-dinitrophenylhydrazine in 6% HCl to give 2,4-dinitrophenylhydrazone. The results are summarized in Table 3.

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