HETEROCYCLES, Vol. 85, No. 5, 2012, pp. 1089 - 1103. © 2012 The Japan Institute of Heterocyclic Chemistry
Received, 19th January, 2012, Accepted, 12th March, 2012, Published online, 22nd March, 2012
DOI: 10.3987/COM-12-12432

SYNTHESES OF 5-AMINO-2-PHENYL-4(3*H)*-PYRIMIDINONE DERIVERTIVES STARTING WITH GLYCINE

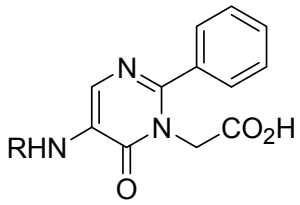
Daisuke Takahashi*, Yutaka Honda, and Kunisuke Izawa*

Research Institute for Bioscience Products and Fine Chemicals, Ajinomoto Co., Inc., 1780 Hinaga, Yokkaichi, Mie, 510-0885, Japan
E-mail:daisuke_takahashi@ajinomoto.com

Abstract - *N*-Cbz derivative of 5-amino-2-phenyl-4(3*H*)-pyrimidinone was prepared from sodium salt of methyl hydroxymethylene glycinate and benzamidine hydrochloride in good yield. However, the reaction with *N*-substituted benzamidine did not proceed to give the desired pyrimidinone. In contrast, the reaction of 4-ethoxymethylene-2-phenyl-5(4*H)*-oxazolone readily prepared from hippuric acid and *N*-substituted benzamidine proceeded nicely to give 5-(benzoylamino)-6-oxo-2-phenyl-1(6*H*)-pyrimidineacetic acid in high yield.

INTRODUCTION

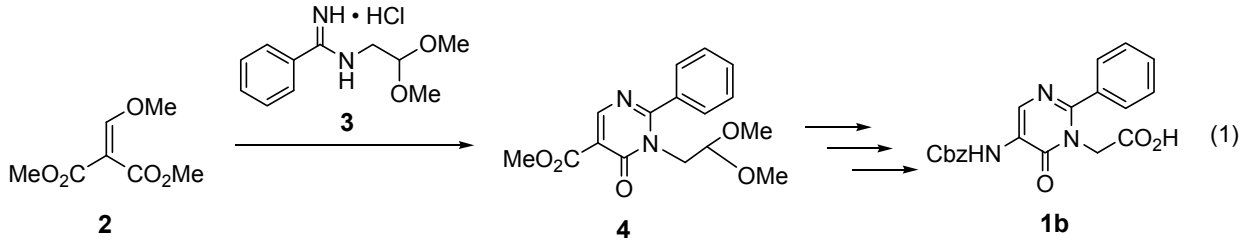
5-Amino-6-oxo-2-phenyl-1(6*H*)-pyrimidineacetic acid (**1a**) has attracted attention as a core molecule for the development of novel nonpeptidic enzyme inhibitors. In particular, several drug candidates such as human leukocyte elastase (also known as human neutrophil elastase) inhibitors for the treatment of COPD (chronic obstructive pulmonary disease)[1] and anti-inflammatory effects,[2] chymase inhibitors for the treatment of heart failure,[3] and serine protease inhibitors for anti-malaria action[4] have been designed and are being developed through the use of **1a** as peptide mimetics for the P2-P3 scaffold of the enzyme, since derivatives of **1a** are known to show high bioavailability.



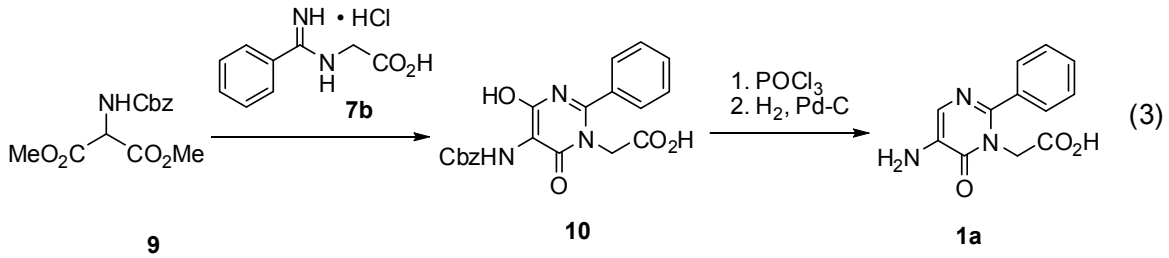
1a R=H
1b R=Cbz
1c R=Bz

Figure 1. 5-Amino-6-oxo-2-phenyl-1(6*H)*-pyrimidineacetic acids.

The first synthesis of **1b** was reported by Veale *et al*.[5] using the reaction of methoxymethylenemalonate (**2**) with *N*-(2,2-dimethoxyethyl)benzamidine (**3**) followed by Curtius rearrangement and subsequent oxidation of aldehyde with $NaClO_2$ to the corresponding acid **1b** (eq.1). So far, this method has been widely used to synthesize many pharmaceutical candidates. However, there is a risk of explosion associated with this process on an industrial scale. To avoid dangerous azide chemistry, Nakai *et al*. transformed the carboxyl group to an amino group by Lossen rearrangement using hydroxamate.[6] Alternatively, Kojima *et al*. reported an efficient method for the synthesis of **1a** consisting of the catalytic reduction of 5-nitropyrimidinone (**8**) prepared from 3-methoxy-2-nitroacrylate (**6**) and benzamidine derivatives **7a** (eq.2).[7]



Recently, new strategies for the synthesis of **1a** were presented in a patent application by Sugiura *et al*.[8] First, they used the reaction of *N*-protected dimethyl aminomalonate with *N*-carboxymethyl benzamidine (**7b**) to prepare 5-(benzyloxycarbonylamino)-4-hydroxy-6-oxo-2-phenyl-1(6*H*)-pyrimidineacetic acid (**10**), which was subjected to chlorination followed by reduction to obtain **1a** (eq. 3).



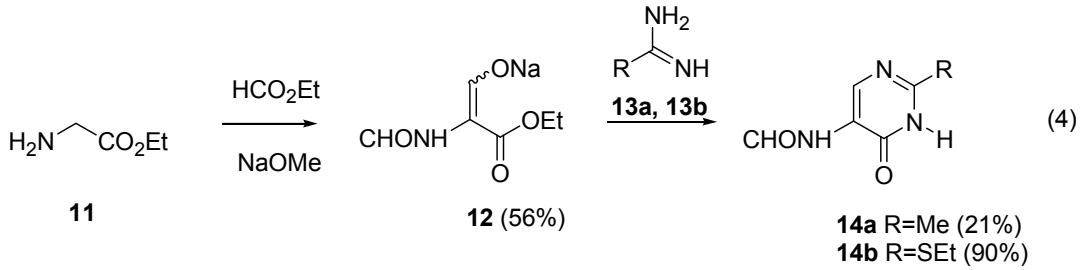
The patent also reported that the reaction of 4-ethoxymethylene-2-phenyl-5(4*H)*-oxazolone with *N*-carboxymethyl benzamidine gave the desired pyrimidinone derivative **1c** in good yield. Since, we have independently developed a method that is very similar to theirs and some of our data are completely novel, in this report we describe our studies on the synthesis of **1a** and **1b** aiming at the production of these compounds on an industrial scale.

RESULTS AND DISCUSSION

Synthetic approach to 1a *via N*-(benzyloxycarbonyl)-2-(hydromethylene)glycinate.

We began our study by using 2-(hydroxymethylene)glycinate as a starting material instead of methoxymethylenemalonate (**2**) or 3-methoxy-2-nitroacrylate (**6**), which require the transformation of carboxylate or nitro groups into an amino substituent via Curtius rearrangement using azide or the reduction of a nitro group in a later step. We considered that our proposed process would be safer by avoiding these risky reagents and hazardous reactions.

Nemeryuk *et al*. reported the synthesis of *N*-formyl ethyl 2-(hydroxymethylene)glycinate **12** by the reaction of ethyl glycinate (**11**) with ethyl formate in the presence of sodium methoxide. Compound **12** was then converted to 5-formamido-4(3*H*)-pyrimidinones (**14a** and **14b**) by the reactions of methyl amidines **13a** (R=Me) and S-ethyl thioisourea **13b** (R=Set) in rather poor and excellent yields, respectively (eq. 4).[9]

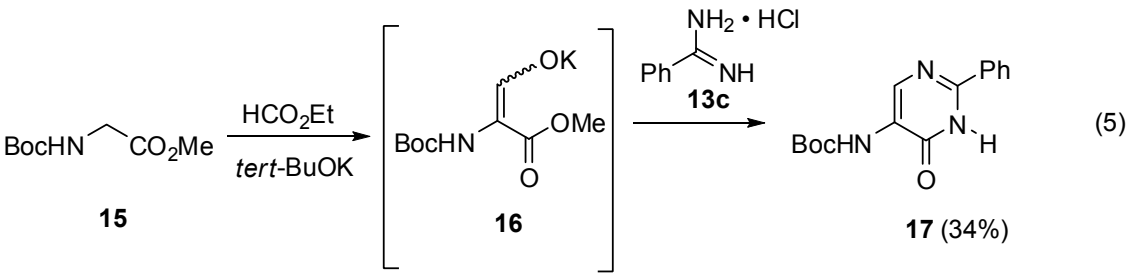


11

12 (56%)

14a R=Me (21%)
14b R=SEt (90%)

We intended to synthesize 5-(*tert*-butoxycarbonylamino)-2-phenyl-4(3*H*)-pyrimidinone **17** in a similar manner from *N*-Boc-glycine methyl ester **15**, which has a more useful protecting group. The reaction of **15** with ethyl formate in the presence of potassium *tert*-butoxide gave (hydroxymethylene)glycinate **16** as a potassium salt, though it was very difficult to isolate as pure crystals in high yield due to high solubility in aqueous solution. Thus, we reacted **16** formed *in situ* with benzamidine hydrochloride (**13c**) to obtain **17** as crystals in 34% isolated yield (eq. 5). We also attempted the synthesis of *N*-Cbz derivative in the same manner, but failed, probably due to cleavage of the *N*-Cbz group under strong basic conditions. As a result, we abandoned this approach toward the synthesis of **1**.



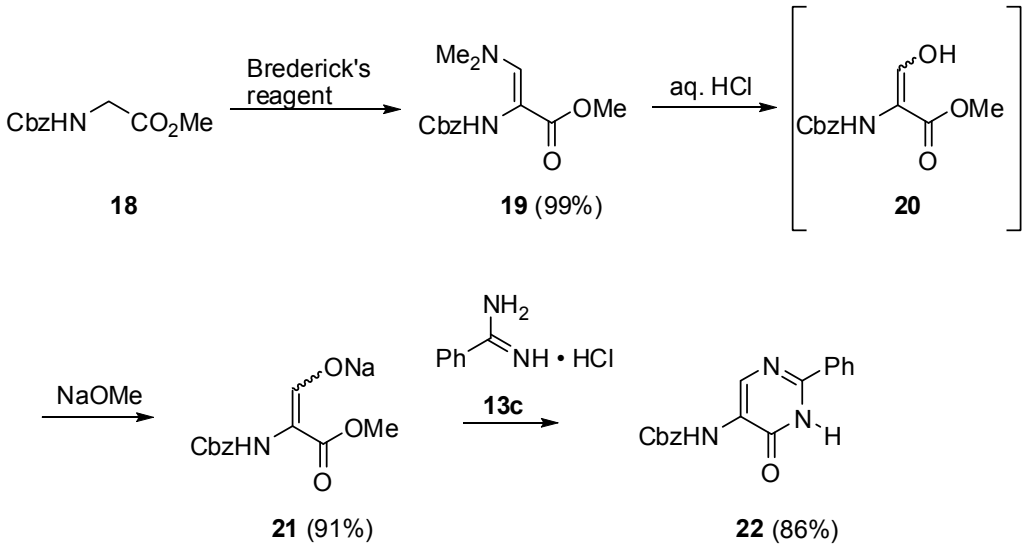
15

16

17 (34%)

To improve the yield in (hydroxymethylene)glycinate formation, we investigated the use of two-step reaction sequences as follows. According to the method reported by Toplak *et al*.,[10]

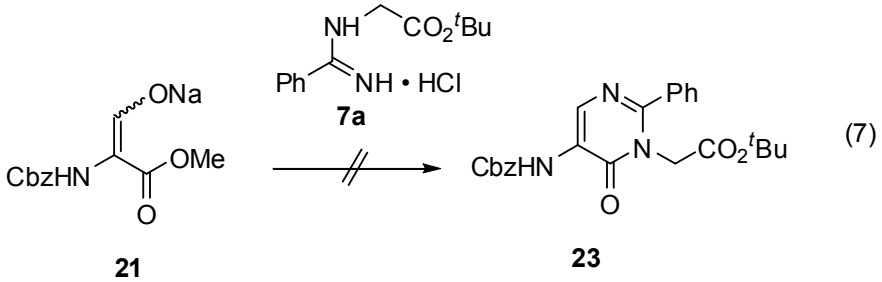
N-Cbz-2-(dimethylaminomethylene)glycinate (**19**) was synthesized from *N*-Cbz-glycine methyl ester (**18**) with *tert*-butoxy-bis(dimethylamino)methane (Brederick's reagent) in almost quantitative yield. Compound **19** has been reported to react with primary alkylamine to give β-alkylamino derivatives in acetic acid.[11] Thus, we examined the reaction of **19** with benzamidine hydrochloride (**13c**) and *N*-*tert*-butoxycarbonylmethyl benzamidine **7a**. Unexpectedly, we found that the desired reactions did not proceed at all in either case. Interestingly, however, sodium salt **21** of methyl (hydroxymethylene)glycinate**,** which is readily prepared from **19** by treatment with diluted hydrochloric acid followed by sodium methoxide, reacted nicely with **13c** to give 5-(benzyloxycarbonylamino)-2-phenyl-4(3*H*)-pyrimidinone (**22**) in very good yield (eq. 6).



18 **19** (99%) **20**

21 (91%) **22** (86%) (6)

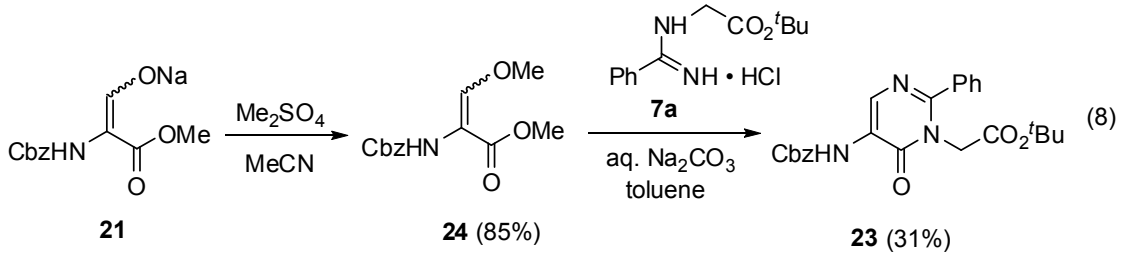
In contrast, the reaction of **21** with *N*-substituted benzamidine **7a** under similar reaction conditions did not proceed to give the desired pyrimidinone **23** (eq. 7).



21 **23** (7)

We speculate that the substitution of benzamidine lowered the reactivity of amidine toward the sodium salt **21**. It has been reported that the alkylation of **22** with ethyl bromoacetate occurs with no selectively to afford the desired ester as a minor product along with the N^1- and *O*-alkylated isomers.[5] We also obtained a very similar result in the reaction of *N*-Boc pyrimidinone **17** with *tert*-butyl bromoacetate.[12]

To achieve efficient pyrimidinone formation, we further investigated the electronic effect of a β-substituent on the reactivity of the olefin bond by changing hydroxymethylene group to methoxymethylene compound **24**, which is readily achieved in 85% yield by the treatment of **21** with dimethyl sulfate.



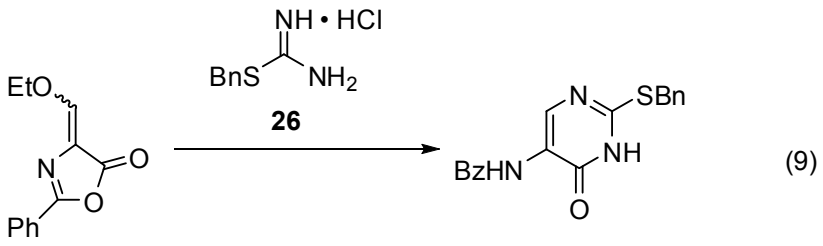
21 **24** (85%) **23** (31%)

Methyl ester **24** was allowed to react with the free form of benzamidine **7a** at 80 °C in toluene to give the desired compound **23** in 31% yield (eq. 8), while the acetoxy compound obtained by acetylation of **21** gave only a trace amount of **23**.

As noted above, the synthetic approach using methyl *N*-Cbz (hydroxymethylene)glycinate (**21**) efficiently gave N^3 non-substituted pyrimidinone **22**, but was not applicable to the industrial-scale synthesis of **23** due to the low yield of cyclization.

Synthesis of 1a *via* 4-hydroxymethylene-5-oxazolone.

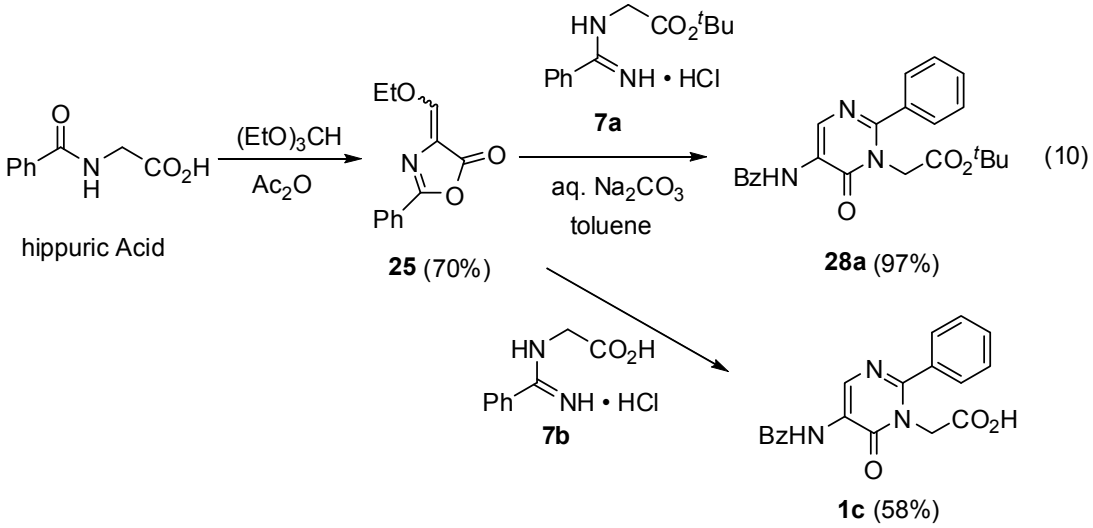
To improve the yield of cyclization of hydroxymethylene glycinate with amidine derivatives, it was considered that the activation of olefin might be essential. We anticipated that 4-alkoxymethylene-5-oxazolone (**25**) may be one of the most suitable intermediates for this purpose.



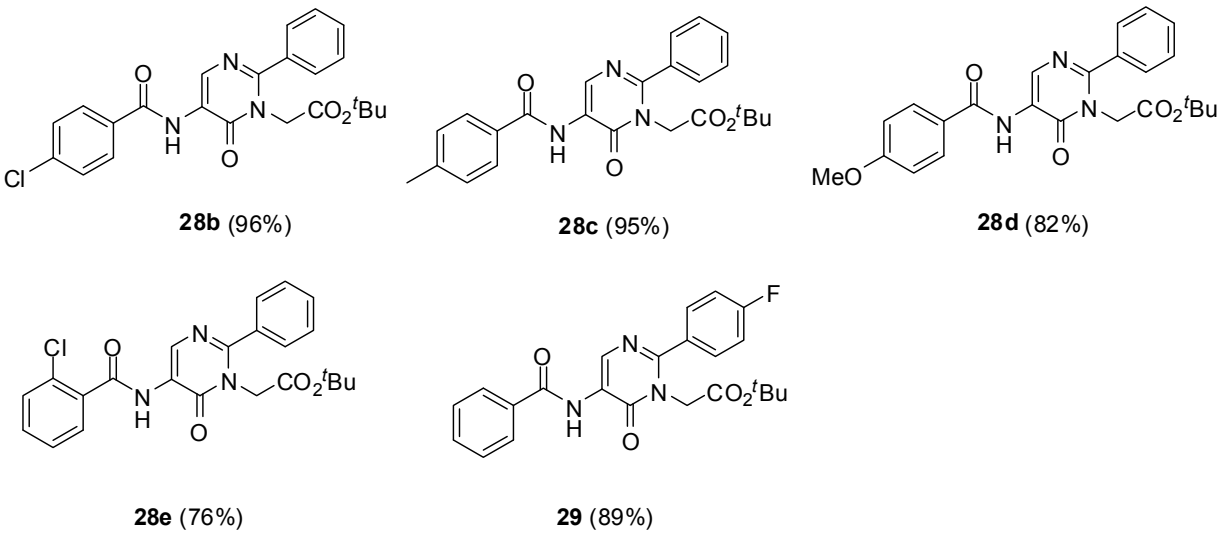
25 **27**

Mukerjee *et al*. reported that the oxazolone **25** reacted with *S*-benzyl isothiouronium hydrochloride salt (**26**) to give 5-benzoylamino-2-benzylsulfanyl-4(3*H*)-pyrimidinone (**27**) in 74% yield (eq. 9).[13] Encouraged by this report, we examined the reaction of **25** with benzamidine derivative, with particular focus on *N*-substituted benzamidine **7a**. Since there have been several reports on the addition-elimination reactions of **25** to replace a β-ethoxy group with a β-amino group,[14] we expected that the risk of a ring-opening reaction by amine attack was low. The oxazolone **25** that was easily prepared from hippuric

acid by the Erlenmeyer method was heated with benzamidine derivative **7a** in toluene after treatment with base to make a free form. To our delight, the desired pyrimidinone **28a** was obtained in 97% yield (eq. 10). The use of *N*-(carboxymethyl)benzamidine **7b** instead of **7a** gave a lower yield (58%) of the product **1c**, while it does not require deprotection of the ester group.[15]

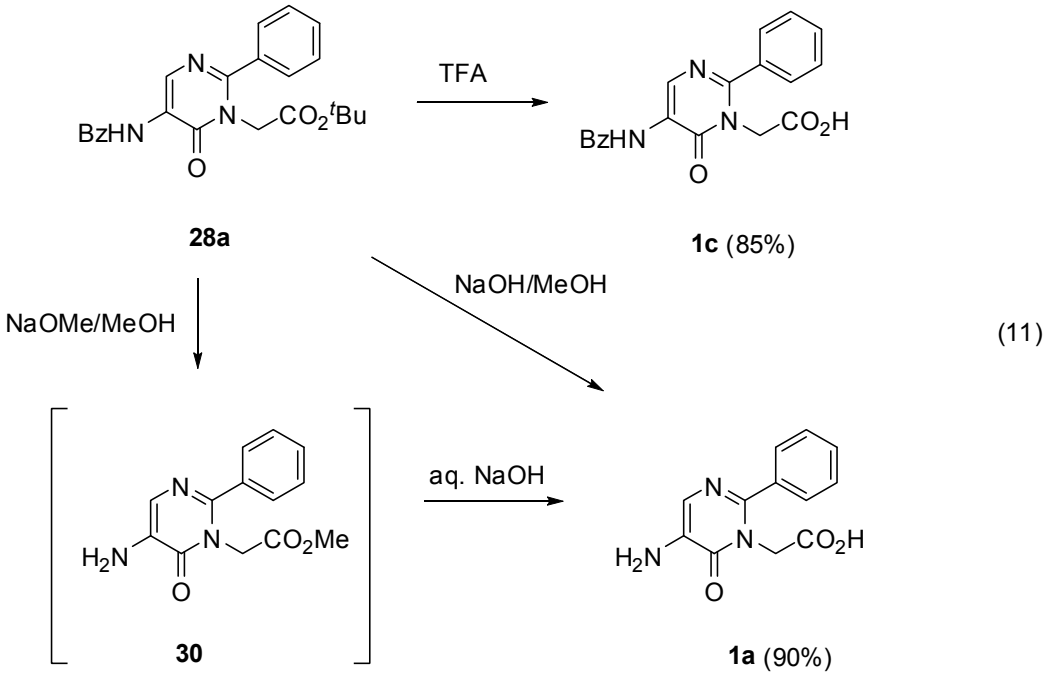


The cyclization reactions using other oxazolones prepared from ring-substituted hippuric acids gave similar results in each case: *p*-Cl **28b**; 96%, *p*-Me **28c**; 95%, *p*-OMe **28d**; 82%, and *o*-Cl **28e**; 76%. The reaction could also be applied to the syntheses of 2-(*p*-fluorophenyl) derivative (**29**; 89%) using the corresponding amidine.



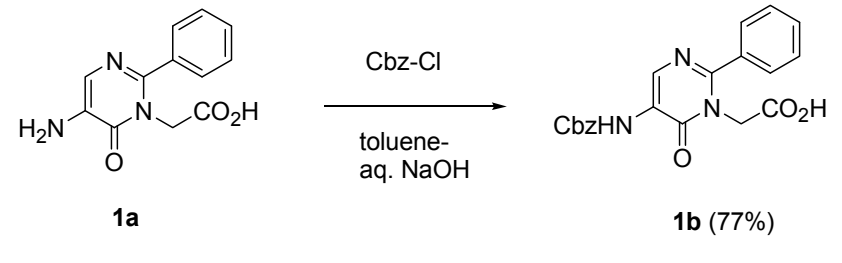
The resulting *t*-butyl ester **28a** was treated with trifluoroacetic acid at ambient temperature to achieve the selective and complete deprotection of *t*-butyl ester followed by recrystallization from ethyl acetate to give pure product **1c** in 85% yield (eq. 11). When we carried out the deprotection reaction by treatment

with NaOMe/MeOH followed by aqueous NaOH solution, we obtained **1a** in only 70% yield along with impurity after conventional acid workup. However, simultaneous cleavage of the *N*-benzoyl and *t*-butyl groups was achieved by refluxing methanol solution of **28a** in the presence of NaOH (3 equiv.) to give **1a** in 90% yield after acid workup.

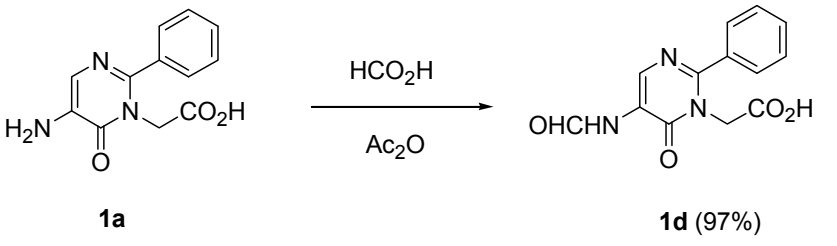


(11)

The pyrimidinone **1a** was treated with benzyl chloroformate under basic conditions using a two-phase reaction to give *N*-Cbz pyrimidinone **1b** in 77% yield. Formylation of **1a** was also efficiently performed by a conventional method to give **1d** in 97% yield.



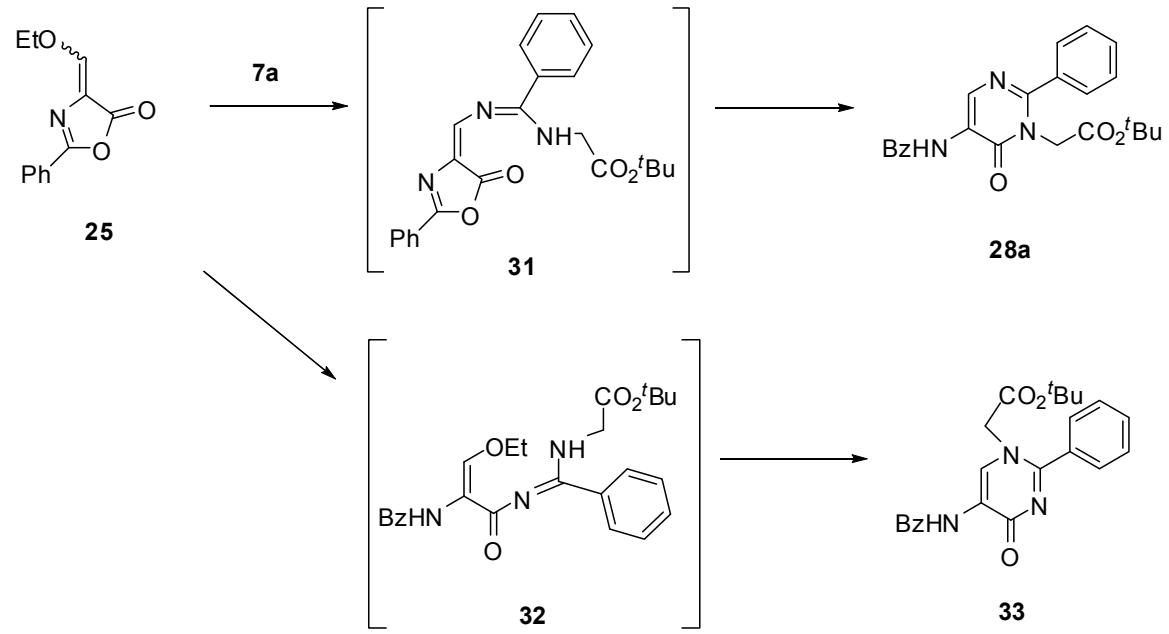
(9)



(10)

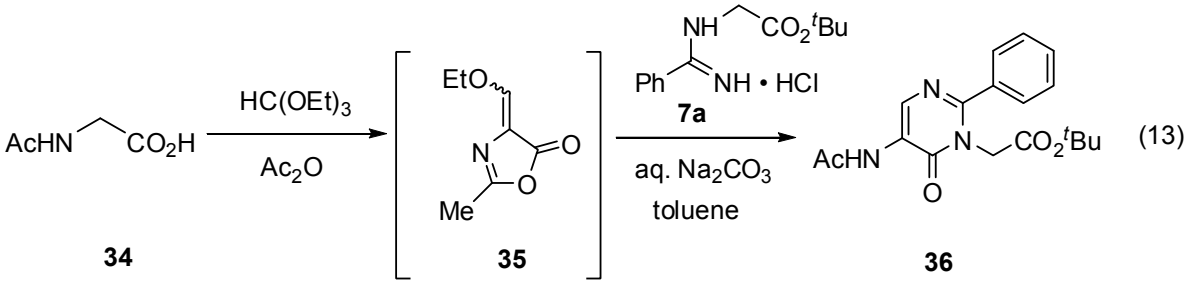
The precise mechanism for the cyclization reaction of ethoxymethylene oxazolone **25** with benzamidinoacetate **7a** is not yet clear. If the nucleophilic attack of an amidine derivative to the

carbonyl carbon at the 5-position occurred, N^1-alkylated pyrimidinone **33** should be formed *via* the intermediate **32**. However, only a trace amount of the product **33** was observed in the reaction mixture. Therefore, the initial attack of the amidine **7a** should occur at the β-position of the exo-olefin bond. This phenomenon is consistent with the result that the ethoxy group of the oxazolone could be changed to an amino group (Scheme 1).



Scheme 1. A possible reaction mechanism for cyclization

Meanwhile, 2-methyl-4-alkoxymethylene-5-oxazolone (**35**) could also be prepared by the treatment of *N*-acetylglycine (**34**) with triethyl orthoformate and acetic anhydride. However, the oxazolone **35** is an oily compound and difficult to obtain in a satisfactory yield. Thus, we attempted to carry out the reaction without the isolation of **35**, and obtained the *N*-acetyl pyrimidinone derivative **36** in 19% overall yield (eq. 13).



Notably, the *N*-acetyl group of **36** can be deacetylated under remarkably mild conditions. Therefore, the *N*-acetyl group should be a very good protecting group if a facile and efficient method for the synthesis of **35** can be developed in the future.[16]

CONCLUSION

Versatile methods for the synthesis of 5-(benzyloxycarbonylamino)-2-phenyl-4(3*H*)-pyrimidinone **22** and its *N3*-carboxymethyl derivative **1b** were developed using glycine as a starting material. The processes do not require hazardous reaction conditions or reagents such as azide and nitro compounds. It should be straightforward to scale-up these processes to an industrial scale.

EXPERIMENTAL

All reagents were purchased and used without further purification. Thin-layer chromatography (TLC) was conducted on precoated TLC plates (Merck 60F250). High-performance liquid chromatography (HPLC) was performed with a Hitachi L-6000 pump and an L-4000 UV detector system using an Inertsil ODS-2 column. Melting points were measured with a Büchi B-545 or a Yanaco melting point apparatus MP model and are uncorrected. NMR spectra were obtained on a Varian XL-300 spectrometer. All proton NMR spectra were measured in $CDCl_3$ or DMSO-d_6 solvent, and chemical shifts are reported as δ values in parts per million relative to tetramethylsilane (δ 0.00) or $CHCl_3$ (δ 7.26) as an internal standard. Data are reported as follows: chemical shift (integrated intensity or assignment, multiplicity, coupling constants in hertz, assignment). All carbon NMR spectra were measured in $CDCl_3$ or DMSO-d_6 solvent, and chemical shifts are reported as δ values in parts per million relative $CDCl_3$ (δ 77.0) or DMSO-d_6 (δ 39.5) as an internal standard. Infrared (IR) spectra were recorded on a SHIMADZU IR Prestige-21 Fourier transform infrared spectrophotometer equipped with a Smith Dura Sample IR II ATR unit and are reported in wave number (cm^{-1}). Mass spectra (MS) were obtained with a ThermoQuest TSQ700 or a JEOL JMS-HX110 instrument with ESI (electrospray) or FAB (fast atom bombardment) ionization. High-resolution mass spectra (HRMS) were obtained with a JEOL MS700V (JEOL Datum Ltd.).

5-(*tert*-Butoxycarbonylamino)-2-phenyl-4(3*H*)-pyrimidinone (17).

To a THF suspension (10 mL) of potassium *t*-butoxide (0.59 g, 5.3 mmol) were added dropwise a THF solution (10 mL) of *N*-Boc-glycine methyl ester (1.00 g, 5.3 mmol) and methyl formate (0.35 g, 6.5 mmol) on an ice bath. After the mixture was stirred for 3 h at the same temperature, benzamidine hydrochloride **13c** (0.82 g, 5.2 mmol) was added. The reaction mixture was stirred at 40 °C for an additional 14 h and concentrated under reduced pressure. The residue was washed with water. The resulting precipitate was triturated with ether, collected and dried to give compound **17** as a white solid (0.52 g, 34%).

Mp 227.5-227.8 °C, IR (neat): 1720, 1647, 1519, 1477, 1153, 711, 617, 565 cm^{-1}, ^{1}H-NMR ($CDCl_3$) δ 1.62 (9H, s), 7.25 (1H, s), 7.52 (3H, m), 8.02 (2H, d, J = 3.0 Hz), 8.82 (1H, s), 11.74 (1H, s), ^{13}C-NMR ($CDCl_3$) δ 28.3, 125.8, 126.7 129.1, 131.4, 132.1, 137.2, 148.5, 152.2, 158.7, HRMS: Calcd for

$C_{15}H_{17}N_3O_3$ $[M+M]^+$: 288.1348, Found: 288.1335.

Methyl *N*-benzyloxycarbonyl-2-(hydroxymethylene)glycinate sodium salt (21).

Methyl *N*-Cbz-2-(dimethylaminomethylene)glycinate (**19**)[10] (2.38 g, 8.55 mmol) was dissolved in MTBE (20 mL). Into the solution was poured aqueous 1M HCl (15 mL) on an ice bath. After the mixture was stirred for 2 h at rt, the organic layer was separated, washed with brine and added dropwise to a 28% NaOMe/MeOH solution (1.50 g, 8.00 mmol). The mixture was concentrated under reduced pressure. The resulting precipitate was triturated with Et_2O, collected and dried to give compound **21** as a white solid (2.12 g, 91%).

Mp 105.8-106.4 °C. IR (neat) 1668, 1556, 1520, 1438, 1278, 1186, 1124, 1055, 734, 694 cm^{-1}. ^{1}H-NMR(DMSO-d_6) δ 3.40 (3H, s), 4.96 (2H, s), 6.83 (1H, s), 7.32-7.37 (5H, m), 8.75 (1H, s), ^{13}C-NMR (DMSO-d_6) δ 48.7, 65.0, 97.2, 126.5, 127.6, 128.3, 137.5, 155.6, 168.7, 172.0., HRMS: Calcd for $C_{12}H_{13}NO_5Na$ $[M+M]^+$: 274.0691, Found: 274.0667.

5-(Benzyloxycarbonylamino)-2-phenyl-4(3*H*)-pyrimidinone (22).

To a solution of sodium salt **21** (1.54 g, 5.62 mmol) in MeCN (19 mL) was added benzamidine hydrochloride **13c** (0.88g) and the mixture was stirred at 70 °C for 14 h. The reaction mixture was concentrated under reduced pressure. To the residue was added water (15 mL) and the mixture was stirred for 1 h. The resulting precipitate was triturated with Et_2O, collected and dried to give compound **22** as a white solid (1.54 g, 86%).

Mp 217.1-218.9 °C, IR (neat); 3315, 1651, 1533, 1502, 1230, 1217, 1049, 949, 765, 687, 600, 569 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 5.18 (2H, s), 7.32-7.57 (8H, m), 8.06-8.09 (2H, m), 8.46 (1H, s), 8.79 (1H, s), 13.0 (1H, brs). ^{13}C-NMR (DMSO-d_6) δ 66.1, 124.8, 127.3, 127.6, 127.9, 128.3, 128.6, 131.1, 132.1, 136.3, 150.9, 153.4, 158.8, 158.9. HRMS: Calcd for $C_{18}H_{15}N_3O_3$ $[M+M]^+$: 322.1191, Found: 322.1163.

Methyl *N*-Cbz-methoxymethylene glycinate (24).

Sodium salt of **21** (300 mg, 1.10 mmol) was suspended in MeCN (5 mL) and dimethyl sulfate (0.105 mL, 1.04 mmol) was added dropwise. The mixture was stirred at 40 °C for 17 h. The resulting precipitate was filtered off and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (hexane-EtOAc) to give **24** as colorless oil (248 mg, 85%).

IR (neat): 3325, 2951, 1701, 1653, 1496, 1249, 1226, 1122, 1053,736, 696 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 3.76 (3H, s), 3.93 (3H, s), 5.10 (1H, s), 5.20 (2H, s), 5.78 (1H, s), 7.28-7.33 (5H, m). ^{13}C-NMR ($CDCl_3$) δ 51.8, 62.1, 67.3, 107.6, 128.2, 128.5, 128.6, 136.2, 155.2, 165.7. HRMS *m/z* Calcd for $C_{13}H_{15}NO_5$ $[M+M]^+$: 266.1028, Found: 266.1031.

5-(Benzyloxycarbonylamino)-6-oxo-2-phenyl-1(6*H*)-pyrimidineacetic acid *tert*-butyl ester (23).

To a suspension of **7a** (675 mg, 2.5 mmol) in toluene (10 mL) was added 10% aqueous solution (8 mL) of sodium carbonate with vigorous stirring. After separation of the organic layer, the aqueous layer was extracted with toluene (5 mL). The combined organic layer was washed with brine and dried over Na_2SO_4. To the organic layer was added **24** (500 mg, 1.9 mmol). The mixture was stirred at 80 °C for 17 h and washed with 1M HCl and brine. After concentration, the residue was purified by silica gel column chromatography (hexane-EtOAc, 10:1 to 2:1) to give **23** as a white solid (246 mg, 31%).

Mp 108.7-108.9 °C; IR (neat) 3265, 1734, 1656, 1514, 1489, 1365, 1213, 1151, 1091, 771, 696 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 1.43 (9H, s), 4.53 (2H, s), 5.17 (2H, s), 7.26-7.54 (10H, m), 8.77 (1H, s). ^{13}C-NMR (DMSO-d_6) δ 27.9, 48.8, 67.5, 83.1, 125.1, 128.1, 128.2, 128.4, 128.6, 128.9, 130.3, 134.1, 134.8, 135.7, 152.7, 153.0, 157.7, 166.1. HRMS: Calcd for $C_{24}H_{25}N_3O_5$ $[M+M]^+$: 436.1872, Found: 436.1875.

5-(Benzoylamino)-6-oxo-2-phenyl-1(6*H)*-pyrimidineacetic acid *tert*-butyl ester (28a).

To a suspension of **7a** (5.00 g, 18.5 mmol) in toluene (70 mL) were added sodium carbonate (8.0 g) and water (70 mL) with vigorous stirring. After phase separation, the aqueous layer was extracted with toluene (70 mL). The combined organic layer was washed with brine and dried over Na_2SO_4. The organic layer was added dropwise to a solution of 2-phenyl-4-ethoxymethylene 5-(4*H)*-oxazolone[17] (**25**) (3.09 g, 14.2 mmol) in MeCN (5 mL). The mixture was stirred at 80 °C for 17 h and washed with 1M HCl, saturated aqueous $NaHCO_3$ solution and brine. After concentration, the residue was added dropwise to hexane and stirred. The resulting crystals were collected by filtration and dried under reduce pressure to give the desired pyrimidinone **28a** as pale yellow crystals (5.59 g, 97%).

Mp 188.5-190.1 °C. IR (neat): 1734, 1649, 1512, 1485, 1365, 1238, 1149, 771, 698, 597 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 1.31 (9H, s), 4.57 (2H, s), 7.51-7.65 (8H, m), 797-8.00 (2H, m), 8.79 (1H, s), 9.58 (1H, s). ^{13}C-NMR ($CDCl_3$) δ 27.9, 49.0, 83.3, 125.2, 125.3, 127.3, 128.2, 128.9, 128.9, 129.0, 130.5, 132.3, 133.7, 153.4, 158.4, 165.6, 166.2. MS(ESI) *m/z*; $[M+M]^+$: 406.2. Anal. Calcd for $C_{23}H_{23}N_3O_4$: C, 68.13; H, 5.72; N, 10.36. Found: C, 68.20; H, 5.65; N, 10.30.

5-(*p*-Chlorobenzoylamino)-6-oxo-2-phenyl-1(6*H)*-pyrimidineacetic acid *tert*-butyl ester (28b).

Yield: 96%; Mp 165.6-168.1 °C. ^{1}H-NMR ($CDCl_3$) δ 1.46 (9H, s), 4.58 (2H, s), 7.42-7.55 (6H, m), 7.86-7.89 (2H, m), 8.76 (1H, s), 9.24(1H, s). ^{13}C-NMR ($CDCl_3$) δ 28.3, 49.4, 83.7, 125.5, 128.5, 129.1, 129.3, 129.5, 130.9, 132.4, 134.4, 137.2, 139.1, 154.0, 158.6, 164.8, 166.5. Anal. Calcd for $C_{23}H_{22}ClN_3O_4$: C, 62.80; H, 5.04; N, 9.55. Found: C, 62.85; H, 5.01; N, 9.48.

5-(*p*-Methylbenzoylamino)-6-oxo-2-phenyl-1(6*H*)-pyrimidineacetic acid *tert*-butyl ester (28c).
Yield 95%; Mp 161.6-163.9 °C. ^{1}H NMR ($CDCl_3$) δ 1.46 (9H, s), 2.43 (3H, s), 4.58 (2H, s), 7.24-7.31 (2H, dd, *J* = 6.5, 1.7 Hz), 7.45-7.54 (6H, m), 7.82-7.85 (2H, dd, *J* = 6.5, 1.7 Hz), 8.79 (1H, s), 9.27 (1H, s). ^{13}C-NMR ($CDCl_3$) δ 21.9, 28.3, 49.4, 83.6, 125.7, 127.7, 128.5, 129.3, 129.9, 130.8, 131.2, 134.5, 136.9, 143.4, 153.6, 158.7, 165.9, 166.6. Anal. Calcd for $C_{24}H_{25}N_3O_4$: C, 68.72; H, 6.01; N, 10.02. Found C, 68.92; H, 5.99; N, 9.92.

5-(*p*-Methoxybenzoylamino)-6-oxo-2-phenyl-1(6*H*)-pyrimidineacetic acid *tert*-butyl ester (28d).
Yield 82%; Mp 160.9-163.6 °C, ^{1}H-NMR ($CDCl_3$) δ 1.46 (9H, s), 3.84 (3H, s), 4.58 (2H, s), 6.96-7.00 (2H, d, *J* = 9.8 Hz), 7.45-7.54 (6H, m), 7.89-7.92 (2H, d, *J* = 9.8 Hz), 8.74 (1H, s), 9.26 (1H, s). ^{13}C-NMR ($CDCl_3$) δ 28.3, 49.4, 55.9, 83.6, 114.4, 125.8, 126.3, 128.6, 129.3, 129.6, 130.8, 134.5, 136.8, 153.5, 158.7, 163.3, 165.5, 166.6. Anal. Calcd for $C_{24}H_{25}N_3O_5$: C, 66.19; H, 5.79; N, 9.65. Found C, 66.23; H, 5.73; N, 9.57.

5-(*o*-Chlorobenzoylamino)-6-oxo-2-phenyl-1(6*H*)-pyrimidineacetic acid *tert*-butyl ester (28e).
Yield 76%; ^{1}H-NMR ($CDCl_3$) δ 1.48 (9H, s), 4.57 (2H, s), 7.32-7.55 (8H, m), 7.89-7.92 (1H, d, *J* = 6.0 Hz), 8.89 (1H, s), 9.27(1H, s). ^{13}C-NMR ($CDCl_3$) δ 27.9, 48.9, 83.2, 125.2, 127.2, 128.2, 128.9, 130.4, 130.5, 130.6, 131.1, 132.1, 134.1, 134.2, 137.2, 153.8, 158.1, 164.7, 166.1. HRMS: Calcd for $C_{23}H_{22}ClN_3O_4$ $[M+M]^+$ 440.1377, Found: 440.1368.

5-(*p*-Fluorobenzoylamino)-6-oxo-2-phenyl-1(6*H*)-pyrimidineacetic acid *tert*-butyl ester (29).
Yield 89%; ^{1}H-NMR ($CDCl_3$) δ 1.46 (9H, s), 4.56 (2H, s), 7.16 (2H, dd, *J* = 8.5 Hz), 7.45-7.56 (4H, m), 7.91 (2H, d, *J* = 7.3 Hz), 8.81 (1H, s), 9.22 (1H, s). ^{13}C-NMR ($CDCl_3$) δ 28.0, 49.0, 83.4, 116.0, 116.3, 125.4, 127.3, 128.9, 130.2, 130.3, 130.4, 132.4, 133.7, 136.5, 152.4, 158.3, 162.2, 165.6, 166.2. HRMS: Calcd for $C_{23}H_{22}FN_3O_4$ $[M+M]^+$: 424.1672, found: 424.1692.

5-(Benzoylamino)-6-oxo-2-phenyl-1(6*H*)-pyrimidineacetic acid (1c).
To a suspension of *N*-carboxymethyl benzamidine (**7b**)[8] (300 mg, 1.68 mmol) in ^{i}PrOH (5 mL) were added 21% NaOEt (631 mg) and 4-ethoxymethylene-2-phenyl-5-oxazolone (**25**) (364 mg, 1.68 mmol), and the mixture was stirred at 80 °C overnight. The solution was concentrated and washed by the addition of water (6 mL) and MTBE (6 mL), and the aqueous layer was adjusted to pH 8 with aqueous NaOH. The aqueous layer was acidified with hydrochloric acid. The precipitate was filtered and dried to give **1c** as pale yellow crystals (324mg, 58%).
Mp 247.0-248.7 °C (lit.,[8] 244.0-245.3 °C). IR (neat) 1728, 1656, 1516, 1487, 1227, 1199, 773, 704, 592

cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 4.56 (2H, s), 7.53-7.65 (8H, m), 7.97 (2H, d, J = 5.1 Hz), 8.81 (1H, s), 9.55 (1H, s). ^{13}C-NMR (DMSO-d_6) δ 48.6, 124.8, 128.0, 128.4, 129.0, 130.7, 132.5, 133.8, 134.4, 140.2, 155.3, 158.1, 165.8, 169.1. Anal. Calcd for C, 65.32; H, 4.33; N, 12.03. Found: C, 65.12; H, 4.18; N, 11.88.

5-Amino-6-oxo-2-phenyl-1(6*H*)-pyrimidineacetic acid (1a).

To a solution of **28a** (1.00 g 2.5 mmol) in MeOH (8 mL) was added NaOH (0.40 g, 10 mmol), and the mixture was stirred under reflux for 17 h. To the reaction mixture was added water (5 mL), and the solution was concentrated under reduced pressure. The residue was poured into MTBE (3 mL) and acidified to pH 3.0 with 6M hydrochloric acid. The resulting precipitates were washed with water/MTBE and dried under reduced pressure to give **1a** as white crystals (585 mg, 96%).

Mp. 202.4-204.7 °C. IR (neat); 2580, 1691, 1616, 1516, 1427, 1382, 1298, 1182, 773, 715, 686, 547 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 4.46 (2H, s), 5.22 (2H, brs), 7.34 (1H, s), 7.41-7.49 (5H, m). HRMS: Calcd for $C_{12}H_{11}N_3O_3$ $[M+M]^+$: 246.0878, Found: 246.0882.

5-(Benzyloxycarbonylamino)-6-oxo-2-phenyl-1(6*H*)-pyrimidineacetic acid (1b).

Sodium salt of compound **1a** (0.56 g, 2.1 mmol) was dissolved in water (6 mL), and benzyl chloroformate (0.43 mL, 2.5 mmol) was added dropwise for 1 h while the pH was maintained at 6-8 by the addition of saturated aqueous $NaHCO_3$ solution. After the mixture was stirred for 2 h, it was washed with toluene. The aqueous layer was acidified to pH 1 with 6M hydrochloric acid and extracted twice with EtOAc. The combined organic layers were washed with brine and concentrated. After the addition of hexane, the resulting precipitate was collected by filtration and dried under reduced pressure to give **1b** (0.61 g, 77%).

Mp 183.6-185.9 °C. IR (neat); 3298, 1734, 1658, 1516, 1491, 1213, 1182, 1086, 986, 767, 748, 694 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 4.52 (2H, s), 5.20 (2H, s), 7.34-7.55 (10H, m), 8.47 (1H, s), 9.01 (1H, s), 13.3 (1H, br). ^{13}C-NMR(DMSO-d_6) δ 48.0, 66.3, 124.7, 127.7, 128.0, 128.4, 128.6, 130.1, 134.1, 136.4, 137.4, 153.4, 153.8, 157.2, 168.7, 169.7. HRMS: Calcd for $C_{20}H_{17}N_3O_5$ $[M+M]^+$: 380.1246, Found: 380.1262.

5-(Formylamino)-6-oxo-2-phenyl-1(6*H*)-pyrimidineacetic acid (1d).

Formic acid (1.5 mL) was added dropwise to acetic anhydride (0.5 mL) at room temperature for 1 h, and **1a** (0.1 g, 0.41 mmol) was then added to the mixture, which was stirred for 2 h. Toluene was added and the mixture was concentrated under reduced pressure. The residue was washed with EtOAc and the resulting crystals were collected by filtration and dried under reduced pressure to give **1d** (0.11 g, 97%).

Mp 218-220 °C. IR (neat): 3282, 1643, 1604, 1512, 1487, 1232, 1186, 1141, 777, 723, 700, 696 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 4.53 (2H, s), 7.49-7.58 (5H, m), 8.14 (1H, s), 8.39 (1H, s), 8.89 (1H, s), 10.05 (1H, s). ^{13}C-NMR (DMSO-d_6) δ 48.5, 124.8, 128.4, 129.0, 130.6, 134.4, 137.2, 154.3, 157.2, 161.2, 163.4,

169.0. HRMS: Calcd for $C_{13}H_{11}N_3O_4$ $[M+M]^+$: 274.0828, Found: 274.0809.

5-(Acetylamino)–6-oxo-2-phenyl-1(6*H*)-pyrimidineacetic acid *tert*-butyl ester (36).

To a suspension of *N*-acetylglycine **34** (0.2 g, 1.7 mmol) in EtOAc (1.5 mL) were added triethyl orthoformate (0.76 g, 5.1 mmol) and acetic anhydride (1.74 g, 16.4 mmol). After the reaction mixture was stirred at 95 ^oC for 14 h, it was cooled to room temperature, and washed with saturated aqueous $NaHCO_3$ solution and brine. After evaporation with toluene, the residue was added to a solution of the free form of benzamidine **7a** (2.22 mmol) and stirred at 80 °C for 15 h. The mixture was washed with 1M hydrochloric acid, saturated aqueous $NaHCO_3$ solution, and brine, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc) to give pyrimidineacetic acid *tert*-butyl ester **36** (0.11 g, 19%) as a pale yellow solid.

Mp; 150-152 °C. IR (neat): 3329, 1735, 1645, 1508, 1354, 1226, 1147, 771, 667, 590 cm^{-1}. ^1H-NMR ($CDCl_3$) δ 1.45 (9H, s), 2.23 (3H, s), 4.54 (2H, s), 7.48 (5H, m), 8.03 (1H, s), 9.09 (1H, s). ^{13}C-NMR (DMSO-d_6) δ 24.4, 27.9, 49.0, 94.1, 125.1, 128.1, 128.9 130.0, 134.0, 136.6, 153.3, 158.0, 166.1, 168.8. HRMS: Calcd for $C_{18}H_{21}N_3O_4$ $[M+M]^+$: 344.1610, Found: 344.1584.

ACKNOWLEDGEMENT

We would like to thanks Mrs. Naoko Hirose for taking analytical data.

REFERENCES (AND NOTES)

1. a) Y. Odagaki, K. Ohmoto, S. Matsuoka, N. Hamanaka, H. Nakai, M. Toda, and Y. Katsuya, *Bioorg. Med. Chem*., 2001, **9**, 647; b) K. Ohmoto, T. Yamamoto, T. Horiuchi, H. Imanishi, Y. Odagaki, K. Kawabata, T. Sekioka, Y. Hirota, S. Matsuoka, H. Nakai, M. Toda, J. C. Cheronis, L. Spruce, A. Gyorkos, and M. Wieczorek, *J. Med. Chem.*, 2000, **43**, 4927.
2. K. Ohmoto, T. Yamamoto, M. Okuma, T. Horiuchi, H. Imanishi, Y. Odagaki, K. Kawabata, T. Sekioka, Y. Hirota, S. Matsuoka, H. Nakai, M. Toda, J. C. Cheronis, L. W. Spruce, A. Gyorkos, and M. Wieczorek, *J. Med. Chem.*, 2001, **44**, 1268.
3. 3a) F. Akahoshi, A. Ashimori, H. Sakashita, T. Yoshimura, M. Eda, T. Imada, M. Nakajima, N. Mitsutomi, S. Kuwahara, T. Ohtsuka, C. Fukaya, M. Miyazaki, and N. Nakamura, *J. Med. Chem*., 2001, **44**, 1297; 3b) S. Takai, D. Jin, M. Nishimoto, A. Yuda, M. Sakaguchi, K. Kamoshita, K. Ishida, Y. Sukenaga, S. Sasaki, and M. Miyazaki, *Life Sci.*, 2001, **69**, 1725.
4. S. Zhu, T. H. Hudson, D. E. Kyle, and A. J. Lin, ***J. Med. Chem.***, 2002, **45**, 3491.
5. C. A. Veale, R. R. Bernstein, C. Bryant, C. Ceccarelli, J. R. Damewood, Jr., R. Earley, S. W. Feeney, B. Gomes, B. J. Kosmider, G. B. Steelman, R. M. Thomas, E. P. Vacek, J. C. Williams, D. J.

Wolanin, and S. J. Woolson, *J. Med. Chem.*, 1995, **38**, 98.

6. K. Ohmoto, T. Yamamoto, T. Horiuchi, T. Kojima, K. Hachiya, S. Hashimoto, M. Kawamura, H. Nakai, and M. Toda, *Synlett.*, 2001, 299.
7. T. Kojima, T. Okada, K. Hachiya, T. Motoi, and S. Hashimoto, PCT Int. Appl. 2001, WO 2001023361.
8. T. Sugiura, T. Horiuchi, T. Miyazaki, T. Kojima, and S. Hashimoto, PCT Int. Appl. 2002, WO 2002051815.
9. M. P. Nemeryuk, A. L. Sedov, T. S. Safonova, A. Cerny, and J. Krepelka, *Coll. Czech. Chem. Comm.*, 1986, **51**, 215.
10. R. Toplak, J. Svete, B. Stanovnik, and S. G. Grdadolnik, *J. Heterocycl. Chem.*, 1999, **36**, 225.
11. R. Toplak, J. Svete, S. G. Grdadolnik, and B. Stanovnik, *Coll. Czech. Chem. Comm.*, 1999, **64**, 177.
12. The reaction of *N*-Boc pyrimidinone **17** with *t*-butyl bromoacetate in aqueous NaOH and MeCN gave the desired *N3*-alkylated compound in 8% yield along with *N1*- (32%) and *O*-alkylated isomers (38%).
13. A. M. Tikdari, P. K. Tripathy, and A. K. Mukerjee, *J. Chem. Soc., Perkin Trans. 1*, 1988, **7**, 1659.
14. M. R. P. Norton Matos, P. M. P. Gois, M. L. E. N. Mata, E. J. Cabrita, and C. A. M. Afonso, *Synth. Commun*., 2003, **33**, 1285.
15. A similar result was independently reported by Sugiura *et al*. (See reference 8) almost the same time as when we submitted our patent application. Preparation of pyrimidine compounds. D. Takahashi, Y. Honda, and K. Izawa, PCT Int. Appl. 2003, WO 2003106434.
16. To be published, D. Takahashi and K. Izawa, US 20050176966.
17. G. Koczan, G. Csik, A. Csampai, E. Balog, S. Bosze, P. Sohar, and F. Hudecz, *Tetrahedron*, 2001, **57**, 4589.