Reaction of Phosgene with the Tricycle Related to the Minor Base of Phenylalanine Transfer Ribonucleic Acids

Taisuke ITAYA* and Tae KANAI

Faculty of Pharmaceutical Sciences, Kanazawa University; Takara-machi, Kanazawa 920–0934, Japan.
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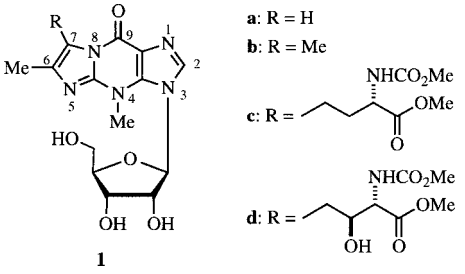
1-Benzylwye (8) underwent electrophilic substitution at the 7-position in the presence of phosgene and pyridine in tetrahydrofuran (THF) to afford the 1,4-dihydropyridines (11, 10, and 14) together with the carboxylic acid 6 and its methyl ester 2 after short treatment of the reaction mixture with methanol and then with water. When triethylamine was used instead of pyridine, phosgene reacted with triethylamine rather than 8, producing (*E*)-3-(diethylamino)propenoyl chloride (17) and diethylcarbamoyl chloride (18).

Key words phosgene; aromatic electrophilic substitution; dihydropyridine; nucleic acid minor base; (chlorocarbonyl)triethylammonium elimination

In the course of our syntheses of the hypermodified nucleosides (**1**)[1—5] of phenylalanine transfer ribonucleic acids, we required methyl 1-benzyl-4,6-dimethyl-9-oxo-4,9-dihydro-1*H*-imidazo[1,2-*a*]purine-7-carboxylate (**2**) in order to elucidate the substituent effect on the stability of the condensed tricycle.[6] We first attempted to obtain the corresponding carboxylic acid **6** by oxidation of 1-benzyl-4,6-dimethyl-9-oxo-4,9-dihydro-1*H*-imidazo[1,2-*a*]purine-7-carbaldehyde.[7] However, this aldehyde resisted oxidation with potassium permanganate in aqueous acetone[8] or hot water,[9] pyridinium dichromate in *N*,*N*-dimethylformamide,[10] Jones reagent,[11] or silver oxide in water[12] or boiling ethanol.[13] Treatment of the aldehyde with a mixture of 30% aqueous hydrogen peroxide and formic acid[14] gave a complex mixture of products.

We next attempted chlorocarbonylation of 1-benzylwye (**8**),[7] which had been utilized as a versatile intermediate for the syntheses of condensed tricyclic minor bases of $tRNAs^{Phe}$.[3,7,15,16] Phosgene reacts with some aromatic rings to afford the corresponding aroyl chlorides in the presence of aluminum chloride.[17] However, we have already reported that the Friedel–Crafts reactions of **8** in the presence of a Lewis acid give unsatisfactory results.[7] On the other hand, Michler reported that *N*,*N*-dimethylaniline reacted with an excess of phosgene to provide 4-(dimethylamino)benzoyl chloride in the absence of a Lewis acid.[18] As our substrate **8** is highly activated at the 7-position toward electrophilic substitution,[3,6,7] the desired acyl chloride **4** (Y=Cl) might be formed from the reaction with phosgene. Thus, we treated **8** with excesses of phosgene and pyridine in tetrahydrofuran (THF) at room temperature for 9 h and then with methanol overnight to obtain the objective methyl ester **2** in 65% yield, together with 32% recovery of **8**. Replacement of the solvent by dichloromethane much accelerated the reaction of **8** with phosgene, giving **2** in somewhat lower yield (50%). Triphosgene could be used instead of phosgene: **2** was obtained in 52% yield together with **8** (38%) in the reaction conducted in dichloromethane.



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The recovery of **8** deserved further investigation because methanol was added to the reaction mixture after **8** had been consumed. TLC analysis of the reaction mixture suggested that the methyl ester **2** was rapidly formed after the addition of methanol, while **8** generated slowly. In a separate run, we obtained a complex mixture of products after short treatment of the reaction mixture with methanol followed by aqueous treatment. The carboxylic acid **6** (10%), the dihydropyridine derivative **11** (2.5%), and the 4-substituted pyridine **9** (0.7%) besides **2** (43%) were obtained. The structures of other compounds that formed were suggested by means of ^{1}H-NMR spectroscopy to be the dihydropyridine derivatives [**10**, **12** (Y=Cl), and **14**] and the acid anhydride **7**. These compounds were obtained in 7%, 4%, 5%, and 7% yields, respectively, together with the carboxylic acid **6** (35%) by treating the reaction mixture with water instead of methanol. The anhydride **7** was alternatively prepared in 30% yield by treatment of **6** with thionyl chloride in chloroform in the presence of triethylamine. To present further evidence to support the anhydride structure for **7**, we treated **7** with methanol in THF in the presence of pyridine at 50 °C for 70 h. We found to our surprise that the product was suggested to be an almost 1 : 1 mixture of the methyl ester **2** and **8** by ^{1}H-NMR spectroscopy. Only a small amount of the carboxylic acid **6** remained in the mixture, indicating that **6** had undergone almost complete decarboxylation. The carboxylic acid **6** indeed underwent facile decarboxylation in methanol at room temperature in the presence of pyridine hydrochloride, providing **8** in quantitative yield probably by the mechanism illustrated in Chart 2. Compound **6** was also quantitatively transformed into **8** by heating at 180 °C. A likely mechanism is illustrated in Chart 3.[19]

Many examples of electrophilic aromatic substitutions leading to dihydropyridines have already been reported for *N*-acylpyridinium and *N*-(alkoxycarbonyl)pyridinium ions.[20—30] Furthermore, it has been reported that phosgene reacts with pyridine to form the carbamoyl chloride **5** through the pyridinium chloride **3**.[31] However, the formation of **12** (Y=Cl), **11**, **10**, **14**, or **9** described above is the first example of aro-

* To whom correspondence should be addressed. e-mail: itaya@mail.p.kanazawa-u.ac.jp

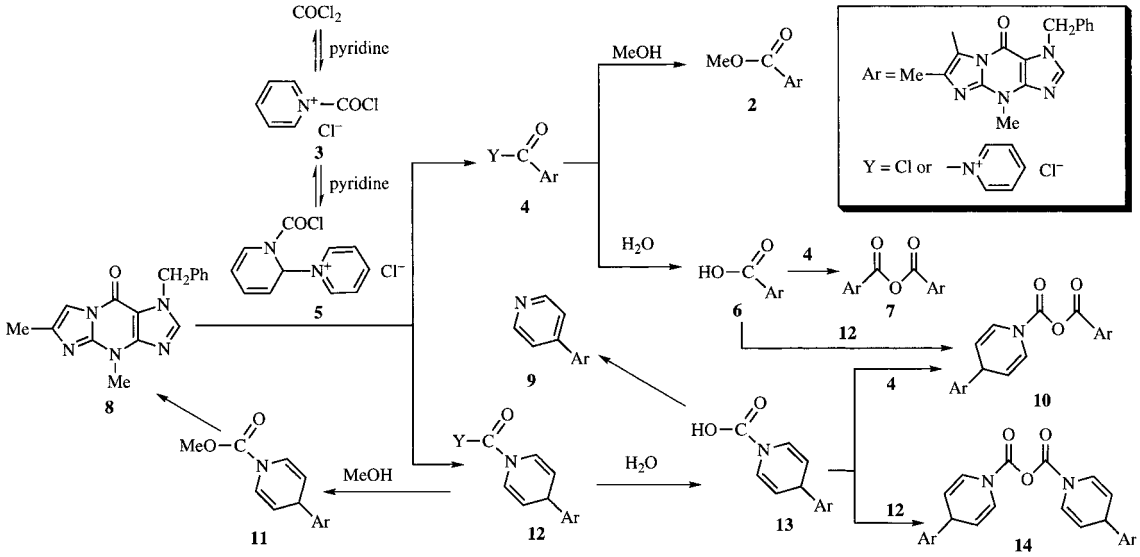

Chart 1

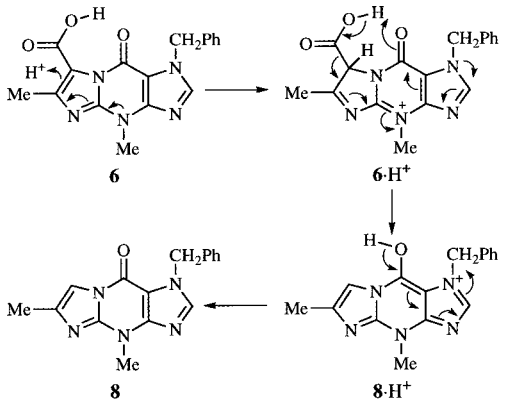

Chart 2

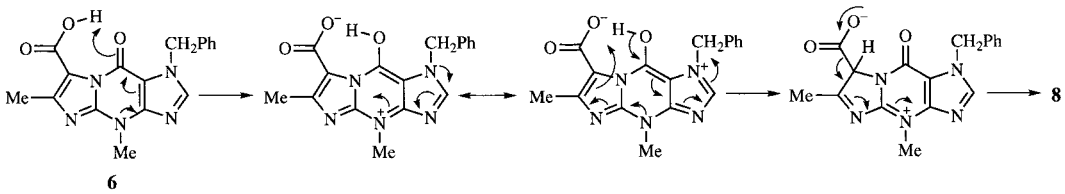

Chart 3

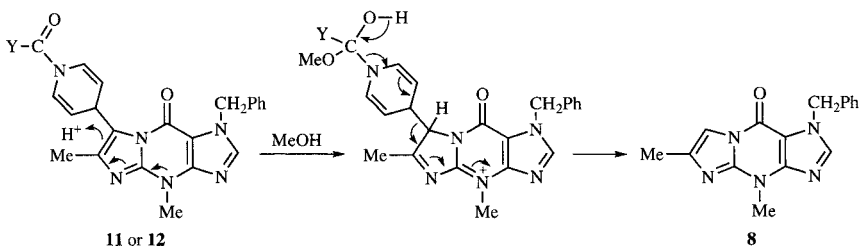

Chart 4

matic substitution with **3** or **5**. When the carbamoyl chloride **12** (Y=Cl) was treated with pyridine hydrochloride in methanol at room temperature for 20 h, **8** was obtained in 50% yield. Compound **8** might be formed directly from **12** and/or through the methyl ester **11** by such a mechanism as illustrated in Chart 4. Compound **11** was indeed transformed into **8** almost quantitatively upon similar treatment. On the other hand, **2** was stable under these conditions. These results

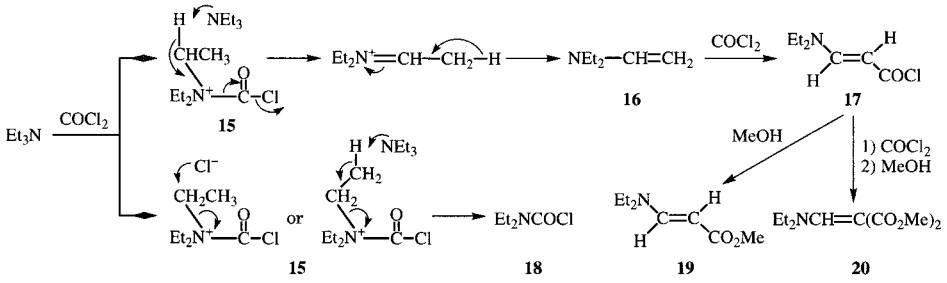

Chart 5

permit us to propose that the reaction of **8** with phosgene in the presence of pyridine followed by treatment with methanol and then with water follows the sequence as shown in Chart 1. Compound **9** was most likely formed from **12** through subsequent hydrolysis, decarboxylation, and oxidation.

We next attempted to improve the yield of **2** by controlling the formation of the dihydropyridine **12**. Triethylamine might be a good substitute for pyridine for this purpose. Somewhat surprisingly, **8** was recovered unchanged in 90% yield on treatment with phosgene in THF in the presence of a large excess of triethylamine at room temperature for 5 h. Instead, methyl (*E*)-3-(diethylamino)propenoate (**19**),[32] dimethyl 2-[(diethylamino)methylidene]propanedioate (**20**),[33] and diethylcarbamoyl chloride (**18**) were obtained in 8%, 6%, and 18% yields, respectively, after treatment of the reaction mixture with methanol. We then treated phosgene with an excess of triethylamine in THF at room temperature in the absence of **8** for 6 h and quenched the reaction with methanol, obtaining **18** (14%), **19** (21%), and **20** (6%). When the solvent was replaced by dichloromethane, the products were shown to be methyl diethylcarbamate (28%) and **18** (12%).

Although the formation of **18** has already been reported for the reaction of phosgene and triethylamine,[34,35] that of a vinylamine derivative such as **16** from triethylamine has not been reported except for the reactions with perhalogenated acyl chlorides[35] including trichloroacetyl chloride,[36,37] trichloroacetic anhydride,[38] or hexachloroacetone.[39] The reaction sequences similar to that delineated in Chart 5 have already been proposed[36,38,39] for these reactions.

In conclusion, we have revealed that 1-benzylwye (**8**) undergoes electrophilic substitution at the 7-position to produce reactive compounds (**4** and **12**) on treatment with phosgene in the presence of pyridine. We have also shown that phosgene activates tertiary amines such as pyridine and triethylamine to produce a variety of compounds, demonstrating that the choice of the base to be employed may be of prime importance for the reactions with phosgene or its analogues.

Experimental

General Notes All melting points were determined by using a Yamato MP-1 or Büchi model 530 capillary melting point apparatus and values are corrected. Spectra reported herein were recorded on a JEOL JMS-SX102A mass spectrometer, a Hitachi model 320 UV spectrophotometer, a Shimadzu FTIR-8100 IR spectrophotometer, a JEOL JNM-EX-270 or a JNM-GSX-500 NMR spectrometer (measured at 25 °C with Me_4Si as an internal standard). MS measurements and elemental analyses were performed by Dr. M. Takani and her associates at Kanazawa University. Flash chromatography was performed according to the reported procedure.[40] The following abbreviations are used: br=broad, d=doublet, m=multiplet, q=quartet, s=singlet, sh=shoulder, and t=triplet.

1-Benzyl-4,6-dimethyl-9-oxo-4,9-dihydro-1*H*-imidazo[1,2-*a*]purine-7-carboxylic Acid Methyl Ester (2) i) By Reaction of Phosgene in THF: A 2 M solution of phosgene in toluene (12.5 ml, 25 mmol) was diluted with dry THF (25 ml) and added to a stirred mixture of **8**[7] (1.47 g, 5 mmol), pyridine (8.1 ml, 0.1 mol), and THF (50 ml) at 0 °C over a period of 15 min. The resulting mixture was stirred at room temperature for 9 h, during which time almost all the starting material **8** was found to be consumed by TLC. Dry methanol (25 ml) was then added to the mixture at 0 °C with stirring, and the whole was stirred at room temperature overnight. The mixture was concentrated *in vacuo*, and the residue was dissolved in dichloromethane (100 ml). The solution was washed successively with water (100 ml), 5% aqueous citric acid (2×100 ml), and saturated aqueous sodium bicarbonate (100 ml), dried over magnesium sulfate, and concentrated *in vacuo.* The residue was purified by flash chromatography [ethyl acetate–ethanol (20 : 1, v/v)] to give **2** (1.14 g, 65%), mp 171.5—176 °C, and **8** (464 mg, 32%), mp 200—206.5 °C. Recrystallization of crude **2** from methanol afforded an analytical sample as faintly yellow prisms, mp 176—177 °C. MS *m/z*: 351 (M^+). UV λ_{max} (95% EtOH) nm (ε): 250 (23700), 285 (sh) (7300), 306 (10500). IR ν_{max} (Nujol) cm^{-1}: 1721, 1696 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 2.49 [3H, s, C(6)-Me], 3.94 (3H, s, NMe or CO_2Me), 3.95 (3H, s, CO_2Me or NMe), 5.62 (2H, s, PhC<u>H</u>$_2$), 7.36 (5H, s, Ph), 7.66 [1H, s, C(2)-H]. *Anal.* Calcd for $C_{18}H_{17}N_5O_3$: C, 61.53; H, 4.88; N, 19.93. Found: C, 61.36; H, 4.92; N, 19.91.

ii) By Reaction of Triphosgene in Dichloromethane: A solution of pyridine (0.28 ml, 3.4 mmol) in dry dichloromethane (2 ml) was added to a solution of **8**[7] (117 mg, 0.399 mmol) and triphosgene (198 mg, 0.667 mmol) in dichloromethane (4 ml) at 0 °C over a period of 20 min, and the resulting suspension was stirred at 0 °C for a further 45 min. Methanol (2 ml) was added to the reaction mixture at 0 °C, and the resulting solution was stored at room temperature for 18 h. The mixture was concentrated *in vacuo*, and the residue was dissolved in dichloromethane (20 ml). The solution was washed successively with water (20 ml), 5% aqueous citric acid (2×20 ml), and saturated aqueous sodium bicarbonate (20 ml), dried over magnesium sulfate, and concentrated *in vacuo*. The residue was purified by flash chromatography [ethyl acetate–ethanol (20 : 1, v/v)] to give **2** (73 mg, 52%), mp 172—175.5 °C, and **8** (45 mg, 38%), mp 200—207.5 °C.

Reaction of 8 with Phosgene in the Presence of Pyridine Followed by Short Treatment with Methanol Compound **8**[7] (352 mg, 1.2 mmol) was treated with phosgene in a manner similar to that described above, and dry methanol (6 ml) was added to the resulting mixture at 0 °C with stirring. The whole was stirred at room temperature for 5 min. The mixture was then partitioned between chloroform and saturated aqueous sodium bicarbonate (50 ml each). The aqueous layer was brought to pH 3 with 10% aqueous phosphoric acid and extracted with chloroform (4×10 ml). The extracts were dried over magnesium sulfate and concentrated *in vacuo* to leave 1-benzyl-4,6-dimethyl-9-oxo-4,9-dihydro-1*H*-imidazo[1,2-*a*]purine-7-carboxylic acid (**6**) (41 mg, 10%), mp 170—180 °C (dec. and resolidified), 206—207 °C. Recrystallization of this product from ethanol afforded an analytical sample of **6** having unchanged mp as colorless needles. MS *m/z*: 337 (M^+), 293 (M^+-CO_2); UV λ_{max} (95% EtOH) nm (ε): 252 (sh) (28400), 256 (31100), 294 (sh) (6900), 312 (8500). IR ν_{max} (Nujol) cm^{-1}: 2561 (OH), 1705, 1648 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 2.74 [3H, s, C(6)-Me], 4.03 (3H, s, NMe), 5.61 (2H, s, PhC<u>H</u>$_2$), 7.38 (5H, m, Ph), 7.87 [1H, s, C(2)-H], 14.48 (1H, br s, CO_2H). *Anal.* Calcd for $C_{17}H_{15}N_5O_3$: C, 60.53; H, 4.48; N, 20.76. Found: C, 60.75; H, 4.38; N, 20.74. On the other hand, the organic layer was washed successively with 5% aqueous citric acid (2×50 ml) and saturated aqueous sodium bicarbonate (50 ml), dried over magnesium sulfate, and concentrated *in vacuo*, leaving a brown foam (451 mg). The residue was purified by flash chromatography [ethyl acetate–ethanol (10 : 1, v/v) and then chloroform–methanol (10 : 1, v/v)] to give a 48 : 7 : 5 (estimated by ^{1}H-NMR

spectroscopy) mixture (298 mg) of **2**, **11**, and **12** (Y=Cl) as a yellow foam from the earlier fraction. From the later fraction was obtained a 1 : 5 : 16 : 23 mixture (70 mg) of **7**, **9**, **10**, and **14** as a brown glass. The mixture of the three compounds was recrystallized from methanol, giving **2** (156 mg), mp 170—173 °C. The mother liquor of recrystallization was concentrated *in vacuo*, and the residue was purified by flash chromatography [ethyl acetate–ethanol (10 : 1, v/v)] followed by preparative TLC on silica gel [1,2-dichloroethane–ethanol (20 : 1, v/v)] to provide a second crop of **2** (24 mg, the total yield was 43%), mp 170—174 °C, and 4-(1-benzyl-4,6-dimethyl-9-oxo-4,9-dihydro-1*H*-imidazo[1,2-*a*]purin-7-yl)-1(4*H*)-pyridinecarboxylic acid methyl ester (**11**) (13 mg, 2.5%), mp 208—213 °C (dec.). Recrystallization of this product from methanol afforded an analytical sample of **11** as colorless needles, mp 211.5—213.5 °C (dec.). MS *m*/*z*: 430 (M^+). UV λ_{max} (95% EtOH) nm (ε): 246 (52700), 318 (5800). IR ν_{max} (Nujol) cm^{-1}: 1715, 1690 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 2.29 [3H, s, C(6)-Me], 3.84 (3H, s, NMe or CO_2Me), 3.89 (3H, s, CO_2Me or NMe), 4.98, 5.05 [1H each, m, dihydropyridine C(β)-H], 5.59 (2H, s, PhC$\underline{H}_2$), 5.84 [1H, m, dihydropyridine C(γ)-H], 6.79, 6.93 [1H each, m, dihydropyridine C(α)-H], 7.36 (5H, m, Ph), 7.64 [1H, s, C(2)-H]. *Anal.* Calcd for $C_{23}H_{22}N_6O_3$: C, 64.17; H, 5.15; N, 19.52. Found: C, 64.13; H, 5.16; N, 19.64. Purification of the mixture of the four compounds described above by repeated preparative TLC on silica gel [1,2-dichloroethane–ethanol (10 : 1, v/v)] afforded 1-benzyl-4,6-dimethyl-7-(4-pyridinyl)-1,4-dihydro-9*H*-imidazo[1,2-*a*]purin-9-one (**9**) (3 mg, 0.7%) as a slightly yellow glass. Recrystallization from methanol afforded an analytical sample of **9** as yellow plates, mp 244—248 °C (dec.). MS *m*/*z*: 370 (M^+). UV λ_{max} (95% EtOH) nm (ε): 234 (29600), 260 (13600), 316 (14400). IR ν_{max} (Nujol) cm^{-1}: 1696 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 2.32 [3H, s, C(6)-Me], 3.99 (3H, s, NMe), 5.57 (2H, s, PhC$\underline{H}_2$), 7.24—7.40 [7H, m, pyridine C(β)-H, Ph], 7.65 [1H, s, C(2)-H], 8.64 [2H, m, pyridine C(α)-H]. *Anal.* Calcd for $C_{21}H_{18}N_6O$: C, 68.09; H, 4.90; N, 22.69. Found: C, 68.13; H, 4.87; N, 22.63.

Reaction of 8 with Phosgene in the Presence of Pyridine Followed by Aqueous Treatment Reaction of **8**[7] (587 mg, 2 mmol) and phosgene was conducted in a manner similar to that described above. Chloroform (100 ml) was added to the resulting mixture, and the solution was extracted with saturated aqueous sodium bicarbonate (3×50 ml). The aqueous layer was brought to pH 3—4 by the addition of 10% aqueous phosphoric acid and then extracted with chloroform (3×50 ml). The extracts were dried over magnesium sulfate and concentrated *in vacuo*, leaving **6** (237 mg, 35%), mp 170—180 °C (dec. and resolidified), 206—207 °C. The organic layer was washed successively with 5% aqueous citric acid (2×100 ml) and saturated aqueous sodium bicarbonate (50 ml), dried over magnesium sulfate, and concentrated *in vacuo*, leaving a brown foam (650 mg). This was purified by flash chromatography [ethyl acetate–ethanol (10 : 1, v/v) and then chloroform–methanol (10 : 1, v/v)]. A yellow glass (97 mg) obtained from the earlier fraction was further purified by preparative TLC on silica gel [chloroform–methanol (30 : 1, v/v)] to give 4-(1-benzyl-4,6-dimethyl-9-oxo-4,9-dihydro-1*H*-imidazo[1,2-*a*]purin-7-yl)-1(4*H*)-pyridinecarbonyl chloride [**12** (Y=Cl)] (37 mg, 4%) as a yellow glass, MS 434, 436 (M^+), 371 (M^+−COCl). ^{1}H-NMR ($CDCl_3$) δ: 2.27 [3H, s, C(6)-Me], 3.91 (3H, s, NMe), 5.23, 5.33 [1H each, m, dihydropyridine C(β)-H], 5.59 (2H, s, PhC$\underline{H}_2$), 5.90 [1H, m, dihydropyridine C(γ)-H], 7.01 [2H, m, dihydropyridine C(α)-H], 7.36 (5H, m, Ph), 7.67 [1H, s, C(2)-H]. 1-Benzyl-4,6-dimethyl-9-oxo-4,9-dihydro-1*H*-imidazo[1,2-*a*]purine-7-carboxylic acid ethyl ester (12 mg, 2%) was also obtained as a slightly yellow glass, ^{1}H-NMR ($CDCl_3$) δ: 1.39 (3H, t, *J*=7 Hz, $\underline{Me}CH_2$), 2.50 [3H, s, C(6)-Me], 3.94 (3H, s, NMe), 4.42 (4H, q, *J*=7 Hz, $MeC\underline{H}_2$), 5.61 (2H, s, PhC$\underline{H}_2$), 7.36 (5H, s, Ph), 7.67 [1H, s, C(2)-H].

A brown foam (332 mg) obtained from the later fraction of the above flash chromatography was further purified by flash chromatography [ethyl acetate–ethanol (3 : 1, v/v)]. The crude product (56 mg) obtained from the earlier fraction was purified by preparative TLC [1,2-dichloroethane–ethanol (10 : 1, v/v)] on silica gel, providing **7** (46 mg, 7%) as a yellow solid, mp 165—177 °C (dec.). Repeated preparative TLC [1,2-dichloroethane–ethanol (10 : 1, v/v)] on silica gel of the crude product (196 mg) obtained from the later fraction afforded **2** (2 mg, 0.3%), **10** (53 mg, 7%), and **14** (40 mg, 5%).

1-Benzyl-4,6-dimethyl-9-oxo-4,9-dihydro-1*H*-imidazo[1,2-*a*]purine-7-carboxylic 4-(1-Benzyl-4,6-dimethyl-9-oxo-4,9-dihydro-1*H*-imidazo[1,2-*a*]-purin-7-yl)-1(4*H*)-pyridinecarboxylic Anhydride (**10**): A yellow glass. FAB-MS *m*/*z*: 736 (MH^+). ^{1}H-NMR ($CDCl_3$) δ: 2.30 [3H, s, C(6″)-Me], 2.60 [3H, s, C(6)-Me], 3.89 [3H, s, N(4″)-Me], 3.97 [3H, s, N(4)-Me], 5.06, 5.25 [1H each, m, dihydropyridine C(β)-H], 5.59 (4H, s, PhC$\underline{H}_2$), 5.89 [1H, m, dihydropyridine C(γ)-H], 6.99 [2H, m, dihydropyridine C(α)-H], 7.34 (10H, m, Ph), 7.65 [1H, s, C(2″)-H], 7.71 [1H, s, C(2)-H].

Bis[4-(1-benzyl-4,6-dimethyl-9-oxo-4,9-dihydro-1*H*-imidazo[1,2-*a*]purin-7-yl)-1(4*H*)-pyridinecarboxylic] Anhydride (**14**): A yellow glass. FAB-MS *m*/*z*: 815 (MH^+). ^{1}H-NMR ($CDCl_3$) δ: 2.30 [6H, s, C(6)-Me], 3.90 [6H, s, N(4)-Me], 5.16, 5.29 [2H each, m, dihydropyridine C(β)-H], 5.59 (4H, s, PhC$\underline{H}_2$), 5.90 [2H, m, dihydropyridine C(γ)-H], 6.72, 6.96 [2H each, m, dihydropyridine C(α)-H], 7.34 (10H, m, Ph), 7.66 [2H, s, C(2)-H].

Bis(1-benzyl-4,6-dimethyl-9-oxo-4,9-dihydro-1*H*-imidazo[1,2-*a*]purine-7-carboxylic) Anhydride (7) A solution of thionyl chloride (0.05 ml, 0.7 mmol) in dry chloroform (0.2 ml) was added to a stirred solution of **6** (100 mg, 0.296 mmol) and triethylamine (0.18 ml, 1.3 mmol) in chloroform (1 ml) at 0 °C over a period of 2 min. The resulting mixture was stirred at room temperature for 21 h, diluted with chloroform (5 ml), extracted with saturated aqueous sodium bicarbonate (2×6 ml), dried over magnesium sulfate, and concentrated *in vacuo*. The residue was purified by flash chromatography [ethyl acetate–ethanol (3 : 1, v/v)] followed by preparative TLC on silica gel [1,2-dichloroethane–ethanol (10 : 1, v/v)] to provide **7** (29 mg, 30%), mp 216—227 °C (dec.). Recrystallization of this product from chloroform–ether (1 : 5, v/v) afforded an analytical sample of **7** as colorless plates, mp 225—231 °C (dec.). MS *m*/*z*: 656 (M^+). UV λ_{max} (95% EtOH) nm (ε): (unstable) 245 nm (*ca.* 32000), 316 (*ca.* 21000). IR ν_{max} (Nujol) cm^{-1}: 1767, 1707 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 2.65 [6H, s, C(6)-Me], 3.96 [6H, s, N(4)-Me], 5.50 (4H, s, PhC$\underline{H}_2$), 7.26 (10H, s, Ph), 7.65 [2H, s, C(2)-H]. ^{1}H-NMR [$(CD_3)_2SO$] δ: 2.44 [6H, s, C(6)-Me], 3.82 [6H, s, N(4)-Me], 5.47 (4H, s, PhC$\underline{H}_2$), 7.15—7.28 (10H, s, Ph), 8.47 [2H, s, C(2)-H]. *Anal.* Calcd for $C_{34}H_{28}N_{10}O_5$: C, 62.19; H, 4.30; N, 21.33. Found: C, 61.92; H, 4.23; N, 21.12.

Aqueous sodium bicarbonate extracts were brought to pH 3—4 by the addition of 10% aqueous phosphoric acid and extracted with chloroform (2×6 ml). The organic layer was dried over magnesium sulfate and concentrated *in vacuo*, leaving **6** (25 mg, 25%), mp 175—185 °C (dec. and resolidified), 202—204 °C.

Acid-Catalyzed Fragmentation of 12 (Y=Cl) Leading to 8 Pyridine (0.7 ml, 8.7 mmol) and 10% hydrogen chloride in methanol (1.6 g, 4.4 mmol) was dissolved in dry methanol to make the whole volume 10 ml. Compound **12** (Y=Cl) (30 mg, 0.069 mmol) was dissolved in this solution (3 ml) and stored at room temperature for 20 h. The resulting solution was concentrated *in vacuo*, and the residue was dissolved in chloroform (5 ml). The solution was washed successively with water (5 ml), 5% aqueous citric acid (2×5 ml), and saturated aqueous sodium bicarbonate (5 ml), dried over magnesium sulfate, and concentrated *in vacuo*, leaving a slightly yellow glass. This was purified by preparative TLC on silica gel [ethyl acetate–ethanol (10 : 1, v/v)] to provide **8** (10 mg, 50%), mp 194—203 °C.

Acid-Catalyzed Fragmentation of 11 Leading to 8 Compound **11** (20 mg, 0.046 mmol) was suspended in the pyridine hydrochloride–pyridine–methanol solution (5 ml) described above, and the mixture was stirred at room temperature for 13 h. The resulting solution was concentrated *in vacuo*, and the residue was dissolved in chloroform (5 ml). The solution was washed successively with 5% aqueous citric acid (2×5 ml) and saturated aqueous sodium chloride (5 ml), dried over magnesium sulfate, and concentrated *in vacuo*, leaving **8** (13 mg, 93%), mp 200—201.5 °C.

Acid-Catalyzed Decarboxylation of 6 Leading to 8 A solution of **6** (20 mg, 0.059 mmol) in the pyridine hydrochloride–pyridine–methanol solution (5 ml) described above was stored at room temperature for 5 h and concentrated *in vacuo*. The solution of the solid residue in chloroform (5 ml) was washed successively with 5% aqueous citric acid (2×5 ml) and saturated aqueous sodium chloride (5 ml), dried over magnesium sulfate, and concentrated *in vacuo*, leaving **8** (17 mg, 100%), mp 205.5—207 °C.

Pyrolytic Decarboxylation of 6 Leading to 8 Compound **6** (20 mg, 0.059 mmol) began to melt with evolving at 180 °C. It was heated at 200 °C for 5 min to resolidify, giving **8** (17 mg, 100%), mp 206—207 °C.

Reaction of Phosgene and Triethylamine i) In THF: A 2 M solution of phosgene in toluene (4.0 ml, 8 mmol) was diluted with dry THF (8 ml) and added to a solution of triethylamine (4.5 ml, 32 mmol) in THF (16 ml) at 0 °C over a period of 15 min. The resulting suspension was stirred at room temperature for 6 h. Dry methanol (8 ml) was added to this suspension with stirring at 0 °C, and the mixture was stirred at room temperature for 1 h. After being stored at room temperature overnight, the mixture was concentrated *in vacuo*. The residual gum was partitioned between ether (50 ml) and saturated aqueous sodium chloride (40 ml). The organic layer was dried over magnesium sulfate and concentrated *in vacuo*, leaving a deep violet oil. This was extracted with hexane (10 ml), and the extracts were purified by flash chromatography [hexane–ethyl acetate (2 : 1, v/v)]. Diethylcarbamoyl chloride (**18**) (155 mg, 14%) was obtained from the fast eluting fraction as a colorless oil, ^{1}H-NMR ($CDCl_3$) δ: 1.21, 1.24 (3H each, t, *J*=7.3 Hz, $\underline{Me}CH_2$),

3.42, 3.49 (2H each, q, J=7.3 Hz, MeC$\underline{H}_2$). Methyl (*E*)-3-(diethylamino)-2-propenoate (**19**)[32] (130 mg, 21%) was obtained from the second fraction, ^{1}H-NMR ($CDCl_3$) δ: 1.16 (6H, t, J=7 Hz, $\underline{Me}CH_2$), 3.19 (4H, q, J=7 Hz, MeC$\underline{H}_2$), 3.66 (3H, s, CO_2Me), 4.57 (1H, d, J=13 Hz, $Et_2NC\underline{H}$), 7.44 (1H, d, J=13 Hz, C$\underline{H}CO_2Me$). Dimethyl 2-[(diethylamino)methylidene]propanedioate (**20**)[33] (35 mg, 6%) was obtained from the third fraction, ^{1}H-NMR ($CDCl_3$) δ: 1.19 (6H, t, J=7 Hz, $\underline{Me}CH_2$), 3.28 (4H, q, J=7 Hz, MeC$\underline{H}_2$), 3.74 (6H, br s, CO_2Me), 7.50 (1H, s, CH=C).

ii) In Dichloromethane: A 2 M solution of phosgene in toluene (1.0 ml, 2 mmol) was diluted with dry dichloromethane (2 ml) and added to a solution of triethylamine (1.12 ml, 8 mmol) in dichloromethane (4 ml) at 0 °C over a period of 5 min. The resulting solution was stored at room temperature for 8 h. Dry methanol (3 ml) was added to this solution, and the mixture was stored at room temperature overnight. The resulting solution was concentrated *in vacuo*. The residual solid was dissolved in dichloromethane (10 ml). The solution was washed successively with water and saturated aqueous sodium bicarbonate (10 ml each), dried over magnesium sulfate, and concentrated *in vacuo*, leaving a 2.3 : 1 mixture of methyl diethylcarbamate [^{1}H-NMR ($CDCl_3$) δ: 1.11 (6H, t, J=7 Hz, $\underline{Me}CH_2$), 3.27 (4H, br, MeC$\underline{H}_2$), 3.69 (3H, s, CO_2Me)] (28%) and diethylcarbamoyl chloride (**18**) (12%) as an orange oil (116 mg).

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