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

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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)propenyl 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-1H-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-1H-imidazo[1,2-a]purine-7-carboxaldehyde.7) However, this aldehyde resisted oxidation with potassium permanganate in aqueous acetone8) or hot water,9) pyridinium dichromate in N,N-dimethylformamide,10) Jones reagent,11) or silver oxide in water12) or boiling ethanol.13) Treatment of the aldehyde with a mixture of 30% aqueous hydrogen peroxide and formic acid14) 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 tRNAsPhe.3,7,15,16) Phosgene reacts with some aromatic rings to afford the corresponding aryl 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.

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 1H-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 1H-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-aclypyridinium 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-
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
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, decarbonylation, and oxidation.

We next attempted to improve the yield of 2 by controlling the formation of the dihydroypyridine 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), 82 dimethyl 2-[(diethylamino)methylene]propanedioate (20), 83,84 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, 82,85 that of a vinylamine derivative such as 16 from triethylamine has not been reported except for the reactions with perchlorinated acyl chlorides 86 including trichloroacetyl chloride, 86,87 trichloroacetic anhydride, 88 or hexachloroacetone. 88 The reaction sequences similar to that delineated in Chart 5 have already been proposed 82,83,89 for these reactions.

In conclusion, we have revealed that 1-benzylhydrazine (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 Me4Si 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-1H-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 (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–methanol (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 248 (95% EtOH) nm (ε): 250 (23700), 285 (sh) (7300), 306 (10500). IR νmax (Nujol) cm⁻¹: 1721, 1696 (C=O). 1H-NMR (CDCl₃): δ: 2.49 (3H, s, C(6)-Me), 3.94 (3H, s, NMe or CO₂Me), 3.95 (3H, s, CO₂Me or NMe), 5.62 (2H, s, PhCH₂), 7.36 (5H, s, Ph), 7.66 (1H, s, C(2)-H). Anal. Calcd for C₁₈H₁₇N₅O₃: 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 (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–methanol (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 (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 treated between chloroform and saturated aqueous sodium bicarbonate (50 ml each). The aqueous layer was brought to pH 7 with 10% aqueous phosphoric acid and extracted with chloroform (4×50 ml). The extracts were dried over magnesium sulfate and concentrated in vacuo. The extract was left to dry benzyl-4,6-dimethyl-9-oxo-4,9-dihydro-1H-imidazo[1,2-a]purine-7-carboxylic acid (4) (41 mg, 10%), mp 170—180 °C (dec. and resolidified), 206—207 °C. Recrystallization of this product from ethanol afforded an analytical sample of 4 with unchanged mp as colorless needles. MS m/z: 337 (M⁺), 293 (M⁺–CO₂), UV 248 (95% EtOH) nm (ε): 252 (sh) (28400), 256 (31100), 294 (sh) (6900), 312 (8500). IR νmax (Nujol) cm⁻¹: 2516 (OH), 1705, 1648 (C=O). 1H-NMR (CDCl₃): δ: 2.74 [3H, s, C(6)-Me], 4.03 (3H, s, NMe), 5.61 (2H, s, PhCH₂), 7.38 (5H, m, Ph), 7.87 [1H, s, C(2)-H], 14.48 (1H, brs, CO₂H). Anal. Calcd for C₁₉H₁₈N₅O₄: C, 50.63; H, 4.48; N, 20.76. Found: C, 50.75; H, 4.38; N, 20.74. On the other hand, the organic layer was partitioned between chloroform and saturated aqueous sodium bicarbonate (20 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 (20 : 1, v/v)] to give 4 (48.7 : 5 (estimated by 1H-NMR).
spectrum) 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–methanol (1:1, 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-1H-imidazo[1,2-a]pyridine-7-yl)-1H-pyrido[1,4-c]pyridine carboxylic 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 (M²). U. V. λ max (95% EtOH nm (ε)) 246 (52700), 318 (58000). IR ν max (Nujol) cm⁻¹: 1715, 1690, 1650, 1580, 1462, 1290, 720, 710. 1H-NMR (CDCl₃) δ: 2.90 (6H, s, C(6)-Me), 3.98 (6H, s, N(4)-Me), 5.39 (1H, d, J = 7 Hz, Me₃C), 5.69 (2H, s, PhCH₂), 7.36 (5H, s, Ph), 7.67 (1H, s, C(2)-H). Anal. Caled for C₂₃H₂₁N₆O₂: C, 71.02; H, 5.59; N, 21.09. Found: C, 70.95; H, 5.61; N, 21.13. From the earlier fraction was obtained an 1:5:1 6:2 3 mixture (298 mg) of a solution of chloroform (100 ml), mp 170—180°C (dec. and resolidified), 206—207°C. The organic layer was washed successively with 5% aqueous citric acid (2x50 ml), saturated aqueous sodium bicarbonate, and concentrated in vacuo, leaving a brown foam (650 mg). This was purified by flash chromatography [ethyl acetate–methanol (10:1, v/v)] and then chloroform–methanol (10:1, v/v)]. A yellow foam (97 mg) obtained from the earlier fraction was purified by preparative TLC on silica gel [1,2-dichloroethane–methanol (30:1, v/v)] to give 4-(1-benzyl-4,6-dimethyl-9-oxo-4,9-dihydro-1H-imidazo[1,2-a]pyridine-7-yl)-1H-pyrido[1,4-c]pyridine carboxylic acid chloride (12 (Y = Cl) (37 mg, 4%) as a yellow glass, MS 434, 436 (M⁺), 371 (M⁺ — COCl) . U. H-NMR (CDCl₃) δ: 2.27 [3H, s, C(2)-Me], 3.91 (3H, s, NMe), 5.23, 5.33 [1H each, m, pyridine C(β-H), Ph], 7.65 [1H, s, pyridine C(α-H)]. Anal. Caled for C₂₂H₁₉N₅O₂: C, 70.89; H, 4.90; N, 22.69. Found: C, 70.83; H, 4.88; N, 22.63.

Reaction of 8 with Phosgene in the Presence of Pyridine Followed by Aqueous Treatment

Reaction of 8 (587 mg, 2 mmol) and phosgene was conducted in a manner similar to that described above. Chloroform (100 ml) was added to the reaction mixture, and the solution was extracted with saturated aqueous sodium bicarbonate (3x50 ml). The aqueous layer was brought to pH 3—4 by the addition of 10% aqueous phosphoric acid and then extracted with chloroform (3x50 ml). The extracts were dried over magnesium sulfate and concentrated in vacuo, leaving 6 (237 mg, 55%), mp 170—180°C (dec. and resolidified), 206—207°C. The organic layer was washed successively with 5% aqueous citric acid (2x100 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–methanol (10:1, v/v)] and then chloroform–methanol (10:1, v/v)]. A yellow foam (97 mg) obtained from the earlier fraction was purified by preparative TLC on silica gel [1,2-dichloroethane–methanol (30:1, v/v)] to give 4-(1-benzyl-4,6-dimethyl-9-oxo-4,9-dihydro-1H-imidazo[1,2-a]pyridine-7-yl)-1H-pyrido[1,4-c]pyridine carboxylic acid chloride (12 (Y = Cl) (37 mg, 4%) as a yellow glass, MS 434, 436 (M⁺), 371 (M⁺ — COCl) . U. H-NMR (CDCl₃) δ: 2.27 [3H, s, C(2)-Me], 3.91 (3H, s, NMe), 5.23, 5.33 [1H each, m, pyridine C(β-H), Ph], 7.65 [1H, s, pyridine C(α-H)]. Anal. Caled for C₂₂H₁₉N₅O₂: C, 70.89; H, 4.90; N, 22.69. Found: C, 70.83; H, 4.88; N, 22.63.

A brown foam (332 mg) obtained from the later fraction of the above flash chromatography was further purified by flash chromatography [ethyl acetate–ethanol (1:1, v/v)] and then chloroform–methanol (1:1, v/v)]. The crude product (113 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-1H-imidazo[1,2-a]pyridine-7-carboxylic acid (14) (10). A yellow glass. FAB-MS m/z: 736 (MH⁺). U. H-NMR (CDCl₃) δ: 2.30 [3H, s, C(6)-Me], 2.60 [3H, s, C(2)-Me], 3.89 [3H, s, N(4’)-Me], 3.97 [3H, s, N(4)-Me], 5.06, 5.25 [1H each, m, pyrididine C(β-H)], 5.59 (4H, s, PhCH₂), 5.89 [1H, m, pyrididine C(α-H)], 6.99 [2H, m, pyrididine C(α-H)], 7.34 (10H, m, Ph), 7.65 [1H, s, C(2’)-H]. 1H-NMR (CDCl₃) δ: 1.21, 1.24 (3H each, t, J = 7.3 Hz, Me₃C).
3.42, 3.49 (2H each, q, J=7.3 Hz, MeCH₂). Methyl (E)-3-(diethylamino)-2-propenoate (19)³) (130 mg, 21%) was obtained from the second fraction, ¹H-NMR (CDCl₃) δ: 1.16 (6H, t, J=7 Hz, MeCH₂), 3.19 (4H, q, J=7 Hz, MeCH₂), 3.66 (3H, s, CO₂Me), 4.57 (1H, d, J=13 Hz, EtNCH₂). 7.44 (1H, d, J=13 Hz, CH₂CO₂Me). Dimethyl 2-[(diethylamino)methylidene]propanedioate (20)³) (35 mg, 6%) was obtained from the third fraction, ¹H-NMR (CDCl₃) δ: 1.19 (6H, t, J=7 Hz, MeCH₂), 3.26 (4H, q, J=7 Hz, MeCH₂), 3.74 (6H, brs, CO₂Me), 7.50 (1H, s, CH₂), 7.38 (1H, d, J=5 Hz, MeCH₂).

ii) In Dichloromethane: A 2 ml 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. 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 diethylcarbamoyl chloride (32) (130 mg, 21%) was obtained from the second fraction, ¹H-NMR: 1.19 (6H, t, J=7 Hz, MeCH₂), 3.19 (4H, q, J=7 Hz, MeCH₂), 3.27 (4H, br, MeCH₂), 3.69 (3H, s, CO₂Me) (28%) and diethylcarbamoyl chloride (18) (12%) as an orange oil (116 mg).

References and Notes
17) Beilstein’s “Handbuch der Organischen Chemie,” 3, 16 (1921).
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