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# Synthesis of Imidazo[1,5-*a*]pyrimidines[1)]

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The synthesis of imidazo[1,5-*a*]pyrimidines from 2-substituted pyrimidin-4(3*H*)-ones is described. 2-[(Acylamino)methyl]-6-methylpyrimidin-4-(3*H*)-ones, prepared by the reaction of *β*-aminocrotonamide with *N*-acylated amino acid esters, were treated with $POCl_3$ to give 2- and 4-chloroimidazo[1,5-*a*]pyrimidines, which reacted with various nucleophiles to afford 2- and 4-substituted imidazo[1,5-*a*]pyrimidines.

**Keywords**——pyrimidin-4(3*H*)-one; phosphorus oxychloride; cyclization; imidazo[1,5-*a*]-pyrimidine; purine analogue; rearrangement; nucleophilic substitution; $^1$H-NMR

In the preceding paper, we reported the reaction of *β*-aminocrotonamide (**1**) with *N*-acylated amino acid esters (**2**) to give 2-acylaminomethyl-6-methylpyrimidin-4(3*H*)-ones (**3**) which, on treatment with polyphosphoric acid (PPA), cyclize to imidazo[1,5-*a*]pyrimidines (**4**) and imidazo[4,5-*b*]pyridines (**5**).[2)] In the present paper, we describe the cyclization of **3** with $POCl_3$ to give 2- and 4-chloroimidazo[1,5-*a*]pyrimidines, and their reactions with various nucleophiles.

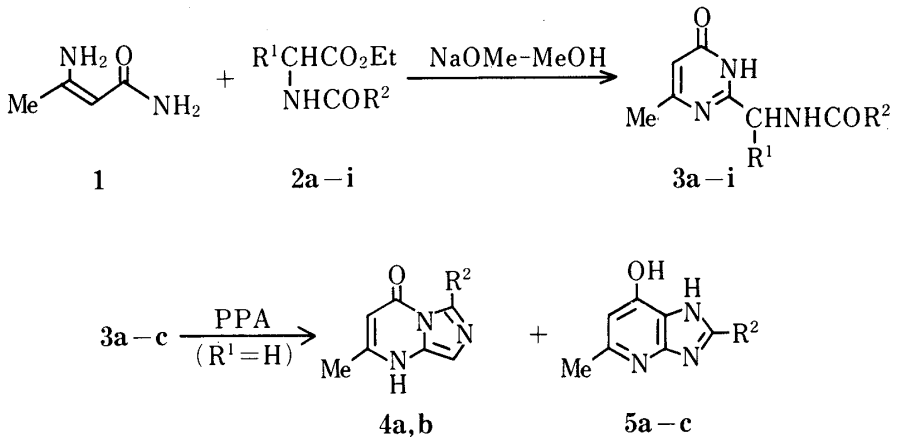


Chart 1

When 2-acetamidomethyl-6-methylpyrimidin-4(3*H*)-one (**3a**) was heated with $POCl_3$ at 90 °C for 1.5 h, 2-chloro-4,6-dimethylimidazo[1,5-*a*]pyrimidine (**8a**) was obtained in 73% yield. On the other hand, the 4-pyrimidinone **3b** was heated with $POCl_3$ at 90 °C for 2 min to give the pyrimidine **6b**, 4-chloro-6-isopropyl-2-methylimidazo[1,5-*a*]pyrimidine (**7b**), and 2-chloro-6-isopropyl-4-methylimidazo[1,5-*a*]pyrimidine (**8b**) in 31, 4, and 37% yields, respectively. Prolonged heating of **3b** at the same temperature gave exclusively **8b** in 71% yield. Similarly, treatment of 4-pyrimidinones (**3c—i**) with $POCl_3$ gave pyrimidines (**6c**, **e**, **g**, **i**), and 4-chloro (**7c—i**), and 2-chloro (**8c—i**) derivatives. The results are summarized in Table I.

As shown in Chart 2, compounds **7** and **8** are presumably formed *via* the pyrimidine **6**. In fact, when compound **6b** was heated with $POCl_3$ at 90 °C for 1.5 h, **7b** and **8b** were obtained in 11 and 88% yields, respectively. Heating of **7b** with $POCl_3$ gave **8b** in 65% yield, indicating

the occurrence of ring transformation of **7b** to **8b**.

On the other hand, **4a**[2] was heated in $POCl_3$ at 90 °C for 10 h to give the 4-chloro compound **7a** and the 2-chloro compound **8a** in 59 and 10% yields, respectively. Compound **4b** was also treated with $POCl_3$ at 90 °C for 40 min to give **7b** as a sole product in 51% yield. Prolonged heating of **4b** at the same temperature gave **7b** and **8b** in 22 and 47% yields, respectively. Heating of **4b** for 18 h gave **8b** in 67% yield (Table II). These chemical reactions also support the rearrangement of **7** to **8**.

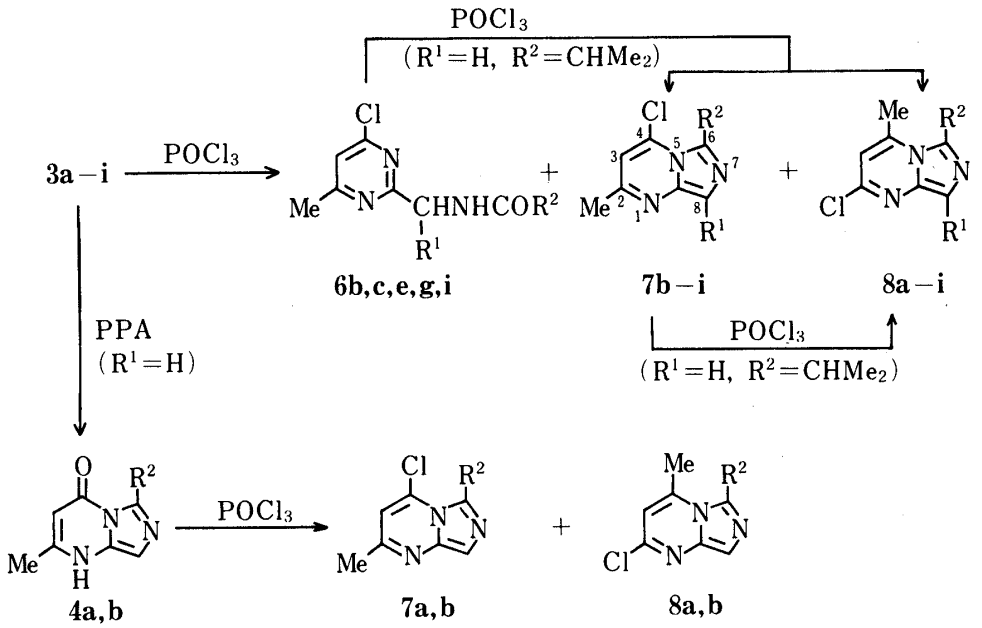


Chart 2

TABLE I. Ring Closure of 4-Pyrimidinones (**3a—i**) with $POCl_3$[a]

| 3 | $R^1$ | $R^2$ | Reaction time (h) | Yield (%) | | |
|---|---|---|---|---|---|---|
| | | | | 6 | 7 | 8 |
| **a** | H | Me | 1.5 | 0 | 0 | 73 |
| **b** | H | $CHMe_2$ | 2 (min) | 31 | 4 | 37 |
| | | | 3.5 | 0 | 0 | 71 |
| **c** | H | Ph | 0.5 | 36 | 3 | 34 |
| | | | 9 | 0 | 2 | 73 |
| **d** | Me | Me | 2 (min) | 0 | 12 | 64 |
| | | | 20 | 0 | 18 | 74 |
| **e** | Me | Ph | 5 (min) | 75 | 4 | 18 |
| | | | 7 | 0 | 9 | 80 |
| **f** | $CH_2Ph$ | Me | 20 (min) | 0 | 12 | 40 |
| | | | 15 | 0 | 16 | 50 |
| **g** | $CH_2Ph$ | Ph | 5 (min) | 67 | 1 | 10 |
| | | | 6 | 0 | 8 | 72 |
| **h** | $CH_2CHMe_2$ | Me | 5 (min) | 0 | 16 | 73 |
| | | | 2.5 | 0 | 16 | 75 |
| **i** | $CH_2CHMe_2$ | Ph | 5 (min) | 73 | 4 | 11 |
| | | | 7 | 0 | 14 | 81 |

a) Each reaction was carried out at 90 °C.

Table II. Chlorination of 6-Substituted 2-Methylimidazo[1,5-*a*]pyrimidin-4(1*H*)-ones (**4a,b**) with $POCl_3$

| 4 | R | Reaction time (h) | Yield (%) | |
|---|---|---|---|---|
| | | | 7 | 8 |
| **a** | Me | 10 | 59 | 10 |
| | | 40 (min) | 51 | — |
| **b** | $CHMe_2$ | 5 | 22 | 47 |
| | | 18 | — | 67 |

The mechanism of the transformation of **7** to **8** may be as illustrated in Chart 3; *i.e.*, the electron-rich nitrogen ($N_7$)[3] reacts with $POCl_3$ to give an intermediate B *via* A. Bond cleavage between the nitrogen ($N_5$) and carbon ($C_6$) of B would give rise to C. The next stage might well involve recyclization to an intermediate D. Elimination of $POCl_3$ from D gives **8**.

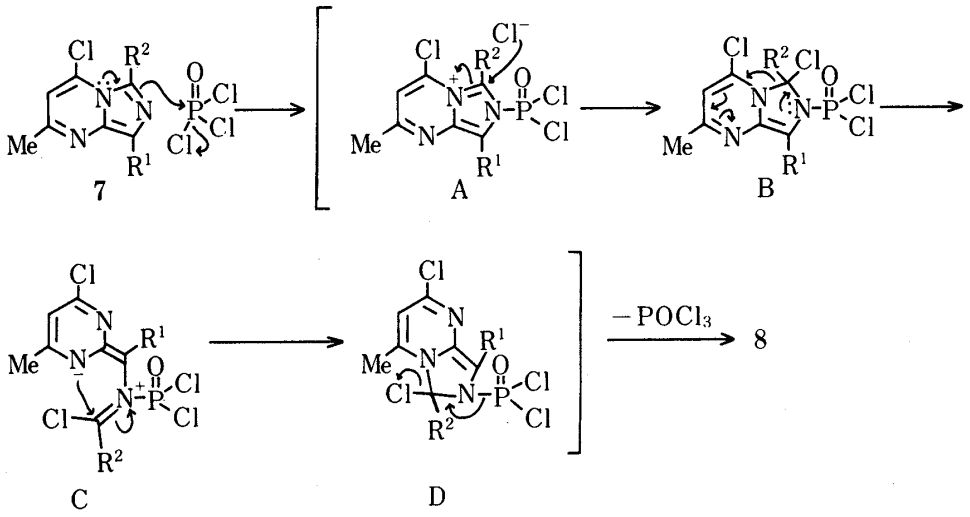


Chart 3

The physical properties of 2-substituted 4-chloro-6-methylpyrimidines (**6b, c, e, g, i**), and 4-chloro-2-methyl-(**7b—i**), and 2-chloro-4-methylimidazo[1,5-*a*]pyrimidines (**8a—i**) are shown in Tables III, IV, and V. In the $^1$H-NMR spectrum of **7** the signal due to the methyl protons at the 2-position was observed at 2.37—2.50 ppm, whereas the $^1$H-NMR spectra of **8a, b, d, f, h** showed the signal due to the methyl protons of 4-position at lower field (2.66—2.82 ppm) because of the effect of the imidazole ring. In contrast, owing to the shielding effect of the benzene ring at the 6-position, the methyl protons at the 4-position of **8c, e, g, i** were observed at higher field (2.07—2.14 ppm).

Next, reactions of **7** and **8** with various nucleophiles were carried out. When the 4-chloro compounds **7b** and **7d** were allowed to react with sodium methoxide in abs. methanol at room temperature for 5 min, the 4-methoxy compounds **9b** and **9d** were obtained in 34 and 76% yields, respectively. On the other hand, the 2-chloro compounds **8a—d** reacted with sodium methoxide at room temperature for 12—24 h to give the corresponding 2-methoxy compounds **12a—d**. Compounds **12b** and **12d** were also obtained by treatment of **8b** and **8d**, respectively, with 10% methanolic sodium hydroxide.

TABLE III. 2-Substituted 4-Chloro-6-methylpyrimidines (**6b, c, e, g, i**)

| 6 | $R^1$ | $R^2$ | mp (°C) | Recryst. solvent | Solvent for column chromatography | $^1$H-NMR ($CDCl_3$) $\delta$ | | Formula | Analysis (%) Calcd (Found) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | 6-Me | 5-H | | C | H | Cl | N |
| **b** | H | $CHMe_2$ | 108—109 | Hexane | Chloroform | 2.52 | 7.11 | $C_{10}H_{14}ClN_3O$ | 52.75<br>(52.88 | 6.20<br>6.17 | 15.57<br>15.81 | 18.45<br>18.67) |
| **c** | H | Ph | 128—129 | Ether | Hexane–ethyl acetate (10 : 1) | 2.52 | 7.10 | $C_{13}H_{12}ClN_3O$ | 59.66<br>(59.80 | 4.62<br>4.69 | 13.55<br>13.84 | 16.06<br>16.08) |
| **e** | Me | Ph | 140—142 | Hexane | Hexane–ethyl acetate (20 : 1) | 2.54 | 7.12 | $C_{14}H_{14}ClN_3O$ | 60.98<br>(61.01 | 5.12<br>5.11 | 12.86<br>13.02 | 15.24<br>15.13) |
| **g** | $CH_2Ph$ | Ph | 138—140 | Benzene–hexane | Hexane–ethyl acetate (15 : 1) | 2.45 | —[a] | $C_{20}H_{18}ClN_3O$ | 68.28<br>(68.40 | 5.16<br>5.06 | 10.08<br>9.79 | 11.94<br>11.85) |
| **i** | $CH_2CHMe_2$ | Ph | 156—158 | Benzene | Hexane–ethyl acetate (10 : 1) | 2.51 | 7.06 | $C_{17}H_{20}ClN_3O$ | 64.25<br>(64.35 | 6.34<br>6.32 | 11.16<br>11.26 | 13.22<br>13.22) |

*a*) The signal could not be distinguished because of overlapping with signals due to benzene ring protons.

TABLE IV. 4-Chloro-2-methylimidazo[1,5-*a*]pyrimidines (**7a—i**)

| 7 | $R^1$ | $R^2$ | mp (°C) | Recryst. solvent | Solvent for column chromatography | $^1$H-NMR ($CDCl_3$) $\delta$ | | Formula | Analysis (%) Calcd (Found) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | 2-Me | 3-H | | C | H | Cl | N |
| **a** | H | Me | 191—192 | Ethyl acetate | Hexane–ethyl acetate (4 : 1) | 2.37 | 6.23 | $C_8H_8ClN_3$ | 52.90 (53.01 | 4.44 4.37 | 19.52 19.35 | 23.14 23.38) |
| **b** | H | $CHMe_2$ | 73—74 | Hexane | Chloroform | 2.43 | 6.47 | $C_{10}H_{12}ClN_3$ | 57.28 (57.54 | 5.77 5.80 | 16.91 16.97 | 20.04 19.78) |
| **c** | H | Ph | 125—126 | Hexane | Hexane–ethyl acetate[a] (20 : 1) | 2.50 | 6.50 | $C_{13}H_{10}ClN_3$ | 64.07 (64.21 | 4.14 4.12 | 14.55 14.51 | 17.24 17.29) |
| **d** | Me | Me | 116—117 | Hexane | Hexane–ethyl acetate (3 : 1) | 2.40 | 6.30 | $C_9H_{10}ClN_3$ | 55.25 (55.31 | 5.15 5.47 | 18.12 18.03 | 21.48 21.50) |
| **e** | Me | Ph | 105—108 | Petroleum ether | Hexane–ethyl acetate (10 : 1) | 2.50 | 6.46 | $C_{14}H_{12}ClN_3$ | 65.25 (65.38 | 4.69 4.46 | 13.76 13.86 | 16.30 16.21) |
| **f** | $CH_2Ph$ | Me | 130—132 | Hexane | Hexane–ethyl acetate (4 : 1) | 2.44 | 6.34 | $C_{15}H_{14}ClN_3$ | 66.30 (66.39 | 5.19 5.25 | 13.05 13.22 | 15.46 15.42) |
| **g** | $CH_2Ph$ | Ph | 140—141 | Petroleum ether | Hexane–ether[a] (15 : 1) | 2.47 | 6.41 | $C_{20}H_{16}ClN_3$ | 71.96 (71.69 | 4.83 5.14 | 10.62 10.68 | 12.59 12.37) |
| **h** | $CH_2CHMe_2$ | Me | 66—69 | Petroleum ether | Hexane–ethyl acetate (4 : 1) | 2.40 | 6.32 | $C_{12}H_{16}ClN_3$ | 60.63 (60.66 | 6.78 6.67 | 14.91 14.80 | 17.68 17.50) |
| **i** | $CH_2CHMe_2$ | Ph | 105—108 | Hexane | Hexane–ether[a] (10 : 1) | 2.48 | 6.40 | $C_{17}H_{18}ClN_3$ | 68.11 (67.91 | 6.05 5.78 | 11.83 11.90 | 14.02 14.49) |

*a*) Alumina column chromatography.

TABLE V. 2-Chloro-4-methylimidazo[1,5-*a*]pyrimidines (**8a—i**)

| 8 | $R^1$ | $R^2$ | mp (°C) | Recryst. solvent | Solvent for column chromatography | $^1$H-NMR ($CDCl_3$) $\delta$ | | Formula | Analysis (%) Calcd (Found) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | 4-Me | 3-H | | C | H | Cl | N |
| **a** | H | Me | 186—188 | Benzene | — | 2.77 | 6.20 | $C_8H_8ClN_3$ | 52.90 (52.84 | 4.44 4.34 | 19.52 19.55 | 23.14 23.04) |
| **b** | H | $CHMe_2$ | 88—89 | Hexane | Chloroform | 2.82 | 6.22 | $C_{10}H_{12}ClN_3$ | 57.28 (57.16 | 5.77 5.79 | 16.91 16.71 | 20.04 20.07) |
| **c** | H | Ph | 189—190 | Benzene | Hexane–ethyl acetate (10 : 1) | 2.14 | 6.27 | $C_{13}H_{10}ClN_3$ | 64.07 (64.12 | 4.14 4.25 | 14.55 14.40 | 17.24 17.06) |
| **d** | Me | Me | 151—152 | Ether | Hexane–ethyl acetate (3 : 1) | 2.72 | 6.10 | $C_9H_{10}ClN_3$ | 55.25 (55.48 | 5.15 5.01 | 18.12 18.08 | 21.48 21.61) |
| **e** | Me | Ph | 118—120 | Hexane–ether | Hexane–ethyl acetate (10 : 1) | 2.12 | 6.23 | $C_{14}H_{12}ClN_3$ | 65.25 (65.53 | 4.69 4.74 | 13.76 13.30 | 16.30 16.31) |
| **f** | $CH_2Ph$ | Me | 115—116 | Hexane | Hexane–ethyl acetate (4 : 1) | 2.66 | 6.07 | $C_{15}H_{14}ClN_3$ | 66.30 (66.34 | 5.19 5.21 | 13.05 13.06 | 15.46 15.53) |
| **g** | $CH_2Ph$ | Ph | 99—102 | Petroleum ether | Hexane–ether[a] (15 : 1) | 2.07 | 6.20 | $C_{20}H_{16}ClN_3$ | 71.96 (71.89 | 4.83 5.08 | 10.62 10.23 | 12.59 12.33) |
| **h** | $CH_2CHMe_2$ | Me | 83—84 | Petroleum ether | Hexane–ethyl acetate (4 : 1) | 2.73 | 6.13 | $C_{12}H_{16}ClN_3$ | 60.63 (60.81 | 6.78 6.81 | 14.91 14.80 | 17.68 17.79) |
| **i** | $CH_2CHMe_2$ | Ph | 57—58 | Acetone–water | Hexane–ether[a] (10 : 1) | 2.12 | 6.23 | $C_{17}H_{18}ClN_3$ | 68.11 (67.93 | 6.05 6.05 | 11.83 11.74 | 14.02 13.99) |

*a*) Alumina column chromatography.

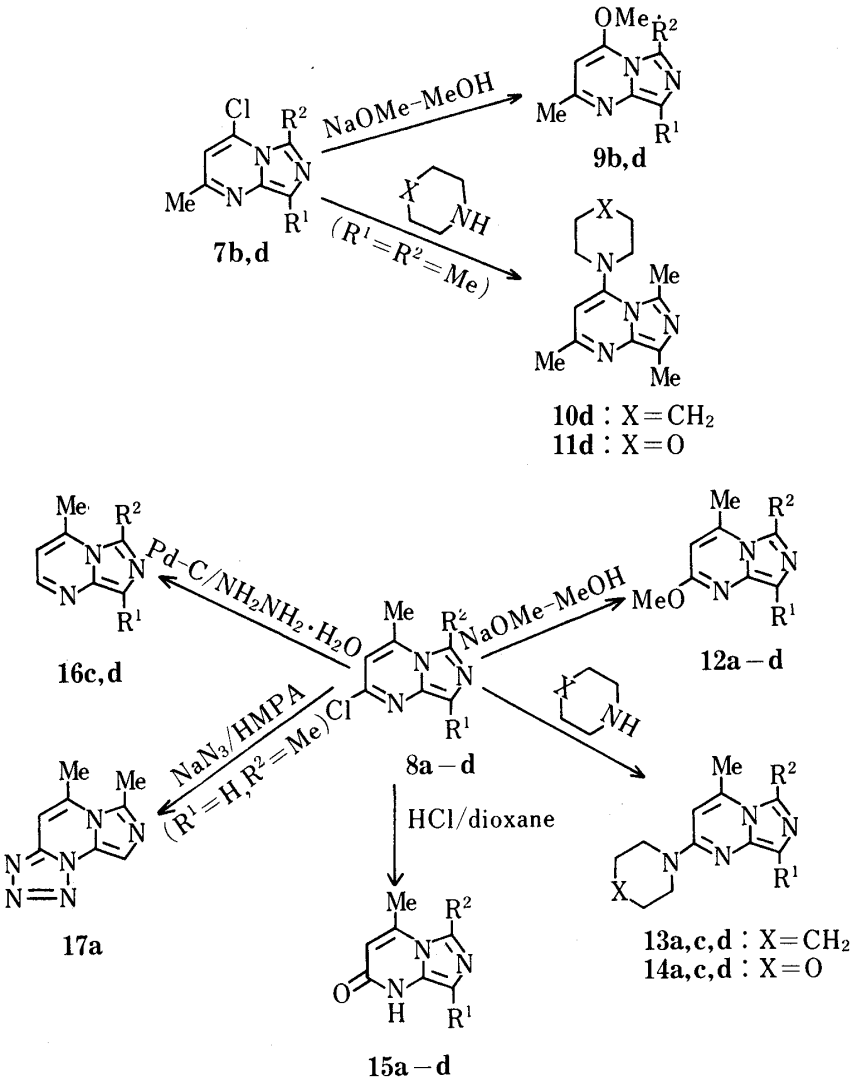


Chart 4

Therefore, the 4-chloro compound **7** seems to be more reactive than the 2-chloro compound **8**, and such reactivity was also observed in the reactions with other nucleophiles. Namely, the 4-chloro compound **7d** reacted with piperidine and morpholine at room temperature for 20 h to give the 4-piperidino (**10d**) and 4-morpholino (**11d**) derivatives in 89 and 87% yields, respectively. However, the 2-chloro compounds **8a**, **c**, **d** did not react with piperidine or morpholine at room temperature, but reacted at 90 °C for 0.5—3 h to give the corresponding 2-piperidino (**13a**, **c**, **d**) or 2-morpholino (**14a**, **c**, **d**) derivatives. The results are summarized in Table VII.

Treatment of **8a—d** with 10% hydrochloric acid in *p*-dioxane gave 4-methylimidazo-[1,5-*a*]pyrimidin-2-ones (**15a—d**). Compounds **15c**, **d** were also obtained by refluxing **8c**, **d** in 10% hydrochloric acid. The results are summarized in Table VIII. Dechlorination of **16c** and **16d** with hydrazine hydrate in the presence of Pd-C gave imidazo[1,5-*a*]pyrimidines **16c** and **16d** in 76 and 65% yields, respectively. Lastly, **8a** reacted with sodium azide in hexamethylphosphoramide (HMPA) to give the tricyclic compound **17a**.

Although a number of purine analogues have been synthesized, few references are available concerning the synthesis of imidazo[1,5-*a*]pyrimidines.[3-5] All these compounds have been synthesized from imidazole derivatives. The advantage of our method is that appropriate substituents can be introduced at the 6- and 8-positions of imidazo[1,5-*a*]-

TABLE VI. 4 (or 2)-Methoxy-2 (or 4)-methylimidazo[1,5-*a*]pyrimidines (**9**, **12**)

| Compd. | $R^1$ | $R^2$ | Yield (%) | mp (°C) | Appearance (Recryst. solvent) | $^1$H-NMR ($CDCl_3$) $\delta$ | | | Formula | Analysis (%) Calcd (Found) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | 2-Me (or 4-Me) | 4-OMe (or 2-OMe) | 3-H | | C | H | N |
| **9b** | H | $CHMe_2$ | 34 | 80—81 | Colorless leaves (Hexane) | 2.42 | 4.04 | 5.60 | $C_{11}H_{15}N_3O$ | 64.37 (64.36 | 7.37 7.44 | 20.47 20.32) |
| **9d** | Me | Me | 76 | 133—134 | Colorless needles (Hexane) | 2.40 | 3.97 | 5.43 | $C_{10}H_{13}N_3O$ | 62.80 (62.96 | 6.85 6.61 | 21.98 21.93) |
| **12a** | H | Me | 72 | 159—160 | Colorless needles (Benzene) | 2.68 | 3.90 | 5.83 | $C_9H_{11}N_3O$ | 61.00 (60.83 | 6.26 6.20 | 23.71 23.52) |
| **12b** | H | $CHMe_2$ | 82 (54)[a)] | 95—96 | Colorless needles (Hexane) | 2.72 | 3.90 | 5.88 | $C_{11}H_{15}N_3O$ | 64.37 (64.67 | 7.37 7.39 | 20.47 20.58) |
| **12c** | H | Ph | 74 | 154—156 | Pale yellow prisms (Ether) | 2.08 | 3.95 | 5.90 | $C_{14}H_{13}N_3O$ | 70.28 (70.46 | 5.48 5.51 | 17.56 17.60) |
| **12d** | Me | Me | 89 (78)[a)] | 87—88 | Pale yellow needles (Hexane) | 2.63 | 3.92 | 5.73 | $C_{10}H_{13}N_3O$ | 62.80 (62.61 | 6.85 6.82 | 21.98 21.74) |

*a*) 10% NaOH–MeOH.

TABLE VII. 2 (or 4)-Methyl-4 (or 2)-piperidino (or morpholino)imidazo[1,5-*a*]pyrimidines (**10d**, **11d**, **13a**, **c**, **d**, **14a**, **c**, **d**)

| Compd. | $R^1$ | $R^2$ | Yield (%) | mp (°C) | Appearance (Recryst. solvent) | $^1$H-NMR ($CDCl_3$) $\delta$ | | Formula | Analysis (%) Calcd (Found) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | 2-Me (or 4-Me) | 3-H | | C | H | N |
| **10d** | Me | Me | 89 | 109—112 | Yellow prisms (Hexane) | 2.40 | 5.72 | $C_{14}H_{20}N_4$ | 68.82 (68.92 | 8.25 8.32 | 22.93 23.04) |
| **11d** | Me | Me | 87 | 149—151 | Yellow needles (Hexane) | 2.42 | 5.78 | $C_{13}H_{18}N_4O$ | 63.39 (63.45 | 7.37 7.21 | 22.75 22.64) |
| **13a** | H | Me | 67 | 133—135 | Yellow needles (Benzene–hexane) | 2.65 | 5.97 | $C_{13}H_{18}N_4$ | 67.79 (67.81 | 7.88 8.14 | 24.33 24.07) |
| **13c** | H | Ph | 75 | 182—184 | Yellow needles (Ethyl acetate) | 2.07 | 6.03 | $C_{18}H_{20}N_4$ | 73.94 (73.79 | 6.90 6.85 | 19.16 19.13) |
| **13d** | Me | Me | 76 | 127—129 | Yellow leaves (Hexane) | 2.61 | 5.87 | $C_{14}H_{20}N_4$ | 68.82 (68.79 | 8.25 8.46 | 22.93 22.84) |
| **14a** | H | Me | 54 | 193—195 | Orange needles (Methanol–ethyl acetate) | 2.68 | 5.92 | $C_{12}H_{16}N_4O$ | 62.05 (61.91 | 6.94 7.11 | 24.12 23.82) |
| **14c** | H | Ph | 82 | 202—205 | Yellow needles (Benzene) | 2.10 | 6.01 | $C_{17}H_{18}N_4O$ | 69.37 (69.25 | 6.16 5.97 | 19.05 18.62) |
| **14d** | Me | Me | 58 | 140—142 | Yellow needles (Ether) | 2.64 | 5.87 | $C_{13}H_{18}N_4O$ | 63.39 (63.31 | 7.37 7.36 | 22.75 22.68) |

TABLE VIII. 6-Substituted 4-Methylimidazo[1,5-*a*]pyrimidin-2-ones (**15a—d**)

| 15 | $R^1$ | $R^2$ | Yield (%) | mp (°C) | Appearance (Recryst. solvent) | IR (KBr) $cm^{-1}$ | $^1$H-NMR (DMSO-$d_6$) $\delta$ | | | Formula | Analysis (%) Calcd (Found) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | 4-Me | 3-H | 8-H | | C | H | N |
| **a** | H | Me | 48 | 265—268 (dec.) | Orange needles (Methanol–ethyl acetate) | 1680 | 2.64 | 5.70 | 6.28 | $C_8H_9N_3O$ | 58.88 (58.87 | 5.56 5.55 | 25.75 25.69) |
| **b** | H | $CHMe_2$ | 28 | 227—229 (dec.) | Orange needles (Ethyl acetate) | 1680[b] | 2.67 | 5.77 | 6.63[d] | $C_{10}H_{13}N_3O$ | 62.81 (63.04 | 6.85 7.01 | 21.97 21.99) |
| **c** | H | Ph | 33 (50)[a] | 258—259 (dec.) | Colorless needles (Ethyl acetate) | 1685[c] | 1.93 | 5.75 | 6.57 | $C_{13}H_{11}N_3O$ | 69.32 (69.11 | 4.92 4.77 | 18.65 18.70) |
| **d** | Me | Me | 55 (66)[a] | 288—290 (dec.) | Pale yellow needles (Methanol–ethyl acetate) | 1665 | 2.55 | 5.63 | — | $C_9H_{11}N_3O$ | 61.00 (60.94 | 6.26 6.22 | 23.72 23.67) |

*a*) 10% HCl only. *b*) $CHCl_3$. *c*) Nujol. *d*) $CDCl_3$.

pyrimidines by using various *N*-acylated amino acid esters.

## Experimental

Melting points are uncorrected. Infrared (IR) spectra were taken with a JASCO A-102 spectrophotometer. Proton nuclear magnetic resonance ($^1$H-NMR) spectra were recorded on a JEOL JNM PMX-60 spectrometer using tetramethylsilane as an internal standard.

**General Procedure for the Ring Closure of 4-Pyrimidinones (3a—i) with $POCl_3$**——A suspension of **3** in $POCl_3$ (ten-fold excess) was heated at 90 °C for 2 min—20 h. After evaporation of excess $POCl_3$ under reduced pressure, the residue was poured into ice-water. The mixture was neutralized with $K_2CO_3$, and extracted with $CHCl_3$. The $CHCl_3$ extract was dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The resulting residue was purified by silica gel or alumina column chromatography to give the pyrimidine **6**, and imidazo[1,5-*a*]pyrimidines **7** and **8**.

**Ring Closure of 4-Chloro-2-[(isobutyrylamino)methyl]-6-methylpyrimidine (6b) with $POCl_3$**——A suspension of **6b** (140 mg, 0.62 mmol) in $POCl_3$ (1.4 g) was heated at 90 °C for 2 h. After evaporation of excess $POCl_3$ under reduced pressure, the residue was poured into ice-water. The mixture was neutralized with $K_2CO_3$, and extracted with $CHCl_3$. The $CHCl_3$ extract was dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give a residue, which was subjected to silica gel column chromatography. Elution with $CHCl_3$ gave **7b** (14 mg, 11%) and **8b** (114 mg, 88%).

**Conversion of 4-Chloroimidazo[1,5-*a*]pyrimidine (7b) to 2-Chloroimidazo[1,5-*a*]pyrimidine (8b)**——A suspension of **7b** (0.1 g) in $POCl_3$ (1 g) was heated at 90 °C for 50 h. After evaporation of excess $POCl_3$ under reduced pressure, the residue was poured into ice-water. The mixture was neutralized with $K_2CO_3$, and extracted with $CHCl_3$. The $CHCl_3$ extract was dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give a crystalline substance. Recrystallization from hexane gave **8b**. Yield, 0.065 g (65%).

**General Procedure for the Chlorination of 6-Substituted 2-Methylimidazo[1,5-*a*]pyrimidin-4(1*H*)-ones (4a, b) with $POCl_3$**——A suspension of **4** (0.5 g) in $POCl_3$ (5 g) was heated at 90 °C for 40 min—18 h. After evaporation of excess $POCl_3$ under reduced pressure, the residue was poured into ice-water. The mixture was neutralized with $K_2CO_3$, and extracted with $CHCl_3$. The $CHCl_3$ extract was dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give a residue. Purification by silica gel column chromatography gave the products **7** and **8**. The results are summarized in Tables II, IV, and V.

**General Procedure for the Synthesis of 4 (or 2)-Methoxy-2 (or 4)-methylimidazo[1,5-*a*]pyrimidines (9b, d, 12a—d)**——1) Compound **7** (or **8**) (0.01 mol) was dissolved in a solution of NaOMe–MeOH, prepared from Na (0.01 g atom) and abs. MeOH (40 ml). The solution was stirred at room temperature for 5 min (or 12—24 h). The reaction mixture was concentrated under reduced pressure to give a residue, which was dissolved in a small amount of water. The resulting solution was neutralized with 10% hydrochloric acid. The crystals precipitated were collected by suction, and recrystallized from an appropriate solvent to give the products **9** and **12**.

2) A solution of **8** (0.01 mol) in MeOH (20 ml) and 10% aqueous NaOH was refluxed for 1—5 h. The reaction mixture was neutralized with 10% hydrochloric acid, and evaporated to dryness under reduced pressure. The residue was extracted with hot $CHCl_3$. The $CHCl_3$ extract was concentrated under reduced pressure to give a crystalline substance, which was recrystallized from an appropriate solvent to give the product **12**.

**2,6,8-Trimethyl-4-piperidino (and morpholino)imidazo[1,5-*a*]pyrimidines (10d, 11d)**——A solution of **7d** (0.1 g, 0.5 mmol) in piperidine (or morpholine) (3 ml) was allowed to stand at room temperature for 20 h. Excess piperidine (or morpholine) was evaporated off under reduced pressure to give a residue, to which was added a small amount of water. The mixture was extracted with $CHCl_3$. The $CHCl_3$ extract was dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give a crystalline substance, which was recrystallized from hexane to give the products **10d** and **11d**.

**General Procedure for the Synthesis of 6-Substituted 4-Methyl-2-piperidino (or Morpholino)imidazo[1,5-*a*]-pyrimidines (13a, c, d, 14a, c, d)**——A solution of **8** (1 mmol) in piperidine (or morpholine) (3 ml) was heated at 90 °C for 0.5—3 h. Excess piperidine (or morpholine) was evaporated off under reduced pressure to give a residue, to which was added a small amount of water. The crystals precipitated were collected by suction, and recrystallized from an appropriate solvent to give the products **13** and **14**. When crystals did not separate out, the mixture was extracted with $CHCl_3$. The $CHCl_3$ extract was dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give a crystalline substance. The results are summarized in Table VII.

**General Procedure for the Synthesis of 6-Substituted 4-Methylimidazo[1,5-*a*]pyrimidin-2(1*H*)-ones (15a—d)**——1) Hydrochloric acid (10%; 25 ml) was added to a solution of **8** (0.005 mol) in *p*-dioxane (20 ml). The mixture was refluxed for 2—6 h. The reaction mixture was neutralized with 10% aqueous NaOH solution, and evaporated under reduced pressure to give a residue, to which was added a small amount of water. The crystals precipitated were collected by suction, and recrystallized from an appropriate solvent to give the product **15**. When crystals did not separate out, the mixture was extracted with $CHCl_3$. The results are summarized in Table VIII.

2) A suspension of **8c, d** (0.2 g) in 10% hydrochloric acid (5 ml) was refluxed for 0.5—3 h. The mixture was neutralized with 10% aqueous NaOH solution. The crystals precipitated were collected, and recrystallized from an appropriate solvent to give the product **15**.

**4-Methyl-6-phenylimidazo[1,5-*a*]pyrimidine (16c)**——Pd-C (10%; 0.11 g) and 80% hydrazine hydrate (1.1 ml) were added to a solution of **8c** (0.2 g, 0.82 mmol) in ethanol (15 ml). The mixture was refluxed for 10 min with stirring. Pd-C was filtered off, and the filtrate was concentrated under reduced pressure to give a residue, to which was added water. The crystals precipitated were collected by suction. Recrystallization from $CHCl_3$–hexane gave the product **16c**, yellow needles, mp 150—151 °C. Yield, 0.13 g, (76%). IR ($CHCl_3$): 1608 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 2.17 (3H, s, ring-Me), 6.27 (1H, d, $J$=4 Hz, ring-H), 7.45 (5H, s, phenyl-H), 7.68 (1H, s, ring-H), 8.00 (1H, d, $J$=4 Hz, ring-H). *Anal.* Calcd for $C_{13}N_{11}N_3$: C, 74.62; H, 5.30; N, 20.08. Found: C, 74.57; H, 5.16; N, 20.07.

**4,6,8-Trimethylimidazo[1,5-*a*]pyrimidine (16d)**——Following the procedure given for **16c**, **8d** (0.3 g, 1.5 mmol) was treated with a mixture of 10% Pd-C (0.2 g) and 80% hydrazine hydrate (2 ml) in ethanol (10 ml) to give the product **16d**, yellow needles (ether), mp 150—152 °C. Yield, 0.16 g (65%). $^1$H-NMR ($CDCl_3$) $\delta$: 2.55 (3H, s, ring-Me), 2.75 (3H, s, ring-Me), 2.92 (3H, s, ring-Me), 6.07 (1H, d, $J$=4 Hz, ring-H), 7.76 (1H, d, $J$=4 Hz, ring-H). *Anal.* Calcd for $C_9H_{11}N_3$: C, 67.05; H, 6.88; N, 26.07. Found: C, 66.85; H, 6.88; N, 25.84.

**5,7-Dimethylimidazo[1,5-*a*]tetrazo[1,5-*c*]pyrimidine (17a)**——A mixture of **8a** (0.6 g, 3.3 mmol) and $NaN_3$ (1.2 g, 18 mmol) in HMPA (40 ml) was warmed at 50 °C for 8 h. The reaction mixture was concentrated under reduced pressure to give a residue, to which was added water. The crystals precipitated were collected by suction. Recrystallization from $CHCl_3$ gave the product **17a**, yellow needles, mp 214 °C (dec.). Yield, 0.18 g (30%). IR (KBr): 1650 $cm^{-1}$. $^1$H-NMR (DMSO-$d_6$) $\delta$: 2.89 (6H, s, ring-Me × 2), 7.16 (1H, s, ring-H), 7.61 (1H, s, ring-H). *Anal.* Calcd for $C_8H_8N_6 \cdot 1/5H_2O$: C, 50.10; H, 4.41; N, 43.82. Found: C, 50.46; H, 4.17; N, 43.40.

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## References and Notes

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