Studies on Pyrimidine Derivatives; XXXV[1]. Iodination of 2-Aminopyrimidines, 4-Aminopyrimidines, and 4-Pyrimidinones with Iodine Chloride *in situ*

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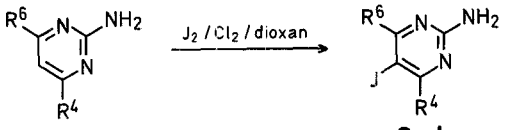
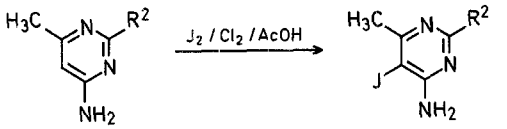
Several papers[2] deal with the preparation of 5-iodopyrimidines by the direct iodination of derivatives having two strongly electron-donating substituents such as amino, hydroxy, mercapto, and methylthio groups. However, practical methods for the synthesis of monoamino- or monohydroxy-5-iodopyrimidines are still unexplored, except for the iodination of 2-amino- and 4-aminopyrimidines with *N*-iodocarboxamide derivatives[3-6]. In the present paper, we describe a simple iodination of 2-amino-, 4-amino-, and 4-hydroxypyrimidines, and the dechlorination of 4-chloro-5-iodopyrimidines to 5-iodopyrimidines.

When chlorine gas was passed at room temperature through the dark red solution of 2-aminopyrimidines **(1a, b)** in dioxan containing an equimolecular amount of iodine the solution gradually became orange in color[7]. Work-up of this mixture afforded the corresponding 2-amino-5-iodopyrimidine **(2a, b)** in 52 and 56% yields, respectively. 4-Aminopyrimidines **(3a–d)** were similarly converted into the 5-iodinated derivatives **(4a–d)** in acetic acid.



1a $R^4 = R^6 = H$
1b $R^4 = R^6 = CH_3$

2a,b



3a $R^2 = H$
3b $R^2 = CH_3$
3c $R^2 = i\text{-}C_3H_7$
3d $R^2 = C_6H_5$

4a-d

4(3*H*)-Pyrimidinones (4-hydroxypyrimidines, **5a–d**) were iodinated in the same manner to give 5-iodo-4(3*H*)-pyrimidinones **(6a–d)** whereas the iodination of 2(1*H*)-pyrimidinones failed; thus, for example, treatment of 2,6-dimethyl-4(3*H*)-pyrimidinone **(5b)** with iodine and chlorine in acetic acid gave 5-iodo-2,6-dimethyl-4(3*H*)-pyrimidinone **(6b)** whereas from the attempted iodination of 4,6-dimethyl-2(1*H*)-pyrimidinone only starting material was recovered.

In addition to these experiments, the 5-iodo derivatives **6a–d** were chlorinated with phosphoryl chloride[8,9] and the hydrodechlorination of the resultant 4-chloro-5-iodopyrimidines **(7a–d)** was investigated in order to find a preparatively useful route to alkyl- or aryl-substituted 5-iodopyrimidines **(8)** which are difficult to prepare by the direct iodination of the corresponding pyrimidines[2]. We found that the Cl-atom in compounds **7a–d** can be conveniently replaced by hydrogen by heating compounds **7** with tosylhydrazine in chloroform and treating the precipitated and isolated 5-iodo-4-tosylhydrazinopyrimidines with aqueous sodium carbonate. Compounds **8a–d** were thus obtained from **7a–d** in high yields.

Table 1. Iodination of 2-Aminopyrimidines (**1**), 4-Aminopyrimidines (**3**), and 4(3*H*)-Pyrimidinones (**5**)

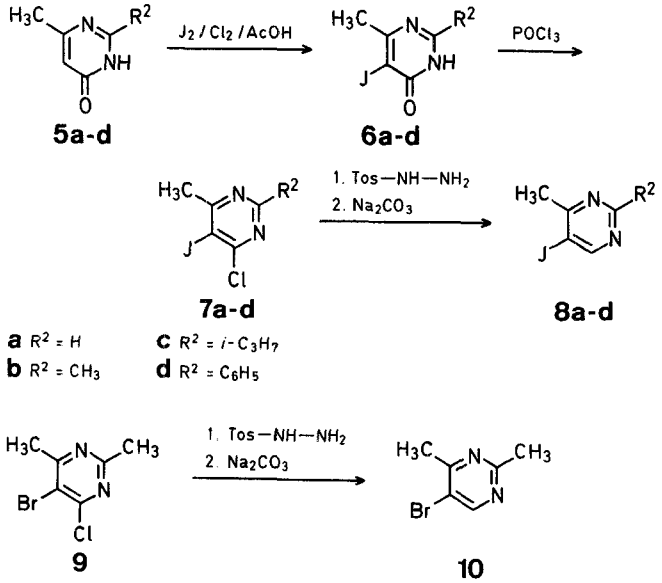
Product	Yield [%]	m.p. [°C]	Molecular formula[a] or m.p. [°C] reported	I.R. ($CHCl_3$) ν [cm^{-1}]	^{1}H-N.M.R. (solvent/TMS_{int})	
					solvent	δ [ppm]
2a	52	223–225° (dec) (ethanol)	224–225°[2]	3530; 3400	CF_3COOH	8.45 (s, 2H)
2b	56	185–186° (acetone)	191–192°[3] 182–183°[4]	3540; 3400	CF_3COOH	2.56 (s, 6H)
4a	47	164–165.5° (methanol)	164–165.5°[9]	3540; 3410	$CDCl_3$	2.60 (s, 3H); 5.65 (s, 2H); 8.33 (s, 1H)
4b	42	141–142° (benzene)	141–142°[4,9] 154–155°[5]	3540; 3410	$CDCl_3$	2.50 (s, 3H); 2.62 (s, 3H); 5.51 (s, 2H)
4c	51	145–147° (hexane)	145–147°[9]	3510; 3400	$CDCl_3$	1.37 (d, 6H, J=7 Hz); 2.56 (s, 3H); 3.00 (sept, 1H); 5.45 (s, 2H)
4d	55	166–167° (cyclohexane)	166–167°[9]	3530; 3410	CF_3COOH	2.90 (s, 3H); 7.4–8.3 (m, 5H)
6a	64	238–239° (dec) (methanol)	238–239° (dec)[4]	3200–2800; 1655	CF_3COOH	2.85 (s, 3H); 9.33 (s, 1H)
6b	56	198–203° (dec) (acetone)	$C_6H_7JN_2O$ (250.0)	3200–2800; 1660	$CDCl_3$	2.46 (s, 3H); 2.51 (s, 3H); 10.5–11.5 (br., 1H)
6c	72	188–189.5° (acetone)	$C_8H_{11}JN_2O$ (278.1)	3200–2700; 1655	$CDCl_3$	1.36 (d, 6H, J=7 Hz); 2.65 (s, 3H); 2.95 (sept, 1H); 12.0–14.0 (br., 1H)
6d	51	249–251° (chloroform)	$C_{11}H_9JN_2O$ (312.1)	3200–2800; 1655	CF_3COOH	2.90 (s, 3H); 7.5–8.3 (m, 5H)

[a] The microanalyses showed the following maximum deviations from the calculated values: C, ±0.33; H, ±0.17; N, ±0.25.

Table 2. 5-Iodopyrimidines (**8**) from 4-Chloro-5-iodopyrimidines (**7**)

Product	Yield [%]	m.p. [°C] or b.p. [°C]/torr	Molecular Formula[a] or Lit. Data	^{1}H-N.M.R. ($CDCl_3$/TMS_{int}) δ [ppm]
8a	77	m.p. 69–70°	$C_5H_5JN_2$ (220.0)	2.66 (s, 3H); 8.87 (s, 1H); 8.93 (s, 1H)
8b	77	m.p. 86–87°	m.p. 81–82°[10]	2.63 (s, 6H); 8.65 (s, 1H)
8c	82	b.p. 115–120°/16	b.p. 125°/18[8]	1.32 (d, 6H, J=6.7 Hz); 2.64 (s, 3H); 3.33 (sept, 1H); 8.68 (s, 1H)
8d	87	m.p. 132–135°	$C_{11}H_9JN_2$ (296.1)	2.72 (s, 3H); 7.3–7.7 (m, 3H); 8.2–8.6 (m, 2H); 8.85 (s, 1H)

[a] The microanalyses showed the following maximum deviations from the calculated values: C, ±0.37; H, ±0.19; N, ±0.16.



This latter hydrodechlorination procedure could also be performed with 5-bromo-4-chloro-2,6-dimethylpyrimidine (**9**) to give 5-bromo-2,4-dimethylpyrimidine (**10**) in 84% yield. The catalytic hydrogenation of compound **9** using palladium on charcoal did not proceed stepwise and 2,4-dimethylpyrimidine was obtained as the main product.

Iodination of 2-Aminopyrimidines (1), 4-Aminopyrimidines (3), and 4(3*H*)-Pyrimidinones (4-Hydroxypyrimidines, 5); General Procedure:
The pyrimidine derivative (**1**, **3**, **5**; 10 mmol) and iodine (1.27 g, 10 mmol) are dissolved in dioxan (30 ml; for **2a, b**) or acetic acid (30 ml, for **3a–d** and **5a–d**). Then, chlorine gas is bubbled through the solution with ice cooling until the iodine color has disappeared. Stirring is continued at room temperature for 30 min and at 60°C for 2–3 h. Then, 10% sodium carbonate solution (20 ml) is added, the organic phase is separated, and evaporated under reduced pressure. The residue is extracted with hot chloroform (100 ml), the chloroform extract evaporated, and the residual product recrystallized from the solvent given in Table 1.

5-Iodopyrimidines (8) from 7; General Procedure:
The 4-chloro-5-iodopyrimidine (**8a–d**; 0.01 mol) and tosylhydrazine (5.59 g, 30 mmol) are heated in boiling chloroform (30 ml) for 12 h. After cooling, the precipitate is isolated by suction and added to aqueous 10% sodium carbonate (20 ml) at 90°C. This mixture is refluxed for 30 min and, after cooling, extracted with chloroform (3 × 30 ml). The extract is dried with potassium carbonate and evaporated and the crude product **8** is purified by distillation, recrystallization, or sublimation.

5-Bromo-2,4-dimethylpyrimidine (10):
5-Bromo-4-chloro-2,6-dimethylpyrimidine (**9**; 2.20 g, 10 mmol) and tosylhydrazine (5.59 g, 30 mmol) are heated in boiling chloroform (30 ml) for 12 h. After cooling, the precipitate is isolated by suction and added to aqueous 10% sodium carbonate (20 ml) at 90°C. This mixture is refluxed for 30 min and, after cooling, extracted with chloroform (3 × 30 ml). The extract is dried with potassium carbonate and evaporated. Sublimation of the residual crude product at 40°C/16 torr gives pure **10** as colorless crystals; yield: 1.57 g (84%); m.p. 41–42°C (Ref.[8], m.p. 42–44°C).

^{1}H-N.M.R. ($CDCl_3$/TMS_{int}): $\delta = 2.62$ (s, 3H); 2.67 (s, 3H); 8.71 ppm (s, 1H).

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