# Photolysis of 5-Iodopyrimidines in Benzene or Heteroarenes; A Convenient Route to 5-Phenyl- and 5-Heteroaryl-pyrimidines

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Photolysis of 5-iodo-, 2-chloro-5-iodo-, and 2,4-dichloro-5-iodo-pyrimidine in solutions of heteroarenes (furan, thiophen, pyrrole, and 1-methylpyrrole) or benzene in acetonitrile affords conveniently and in high yield the corresponding 5-(2-heteroaryl)- and 5-(phenyl)-pyrimidines (1)—(3) (X = O, S, NH, NMe, or CH=CH). Only for those photolyses carried out in thiophen are small amounts of the 3-heteroaryl isomers formed. In contrast, photolysis of the relatively unstable 4-chloro-5-iodopyrimidine in solutions of the above heteroarenes or benzene in acetonitrile gives only low yields of the 4-chloro-5-substituted pyrimidines.

RECENTLY there have been a number of reports of the synthesis of 5-substituted pyrimidines, particularly with reference to the synthesis of nucleoside analogues having antiviral activity.[1-7] However, few quantitative studies of electronic effects of the substituent at position 5 of the pyrimidine ring appear to have been made.[8] As far as we are aware, the only significant study is that of Brown *et al.*,[9] who investigated the dependence of the rate of thermal isomerisation of 2-methoxypyrimidines on the nature of the 5-substituent. We have been interested in the electronic effects of heteroaryl and substituted phenyl groups at the 5-position of the pyrimidine ring on the rate of quaternisation at the ring nitrogen atoms, and also on the rate of nucleophilic displacement of halogen at the 2-position of pyrimidine, and our kinetic studies will be reported in subsequent publications.

In this paper we report simple high yield photochemical synthetic routes to a series of 5-heteroarylpyrimidines

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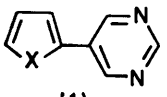
(1; X = O, S, or NMe) and 5-phenylpyrimidine, and also to the corresponding 5-substituted 2-chloro- and 5-substituted 2,4-dichloro-pyrimidines (2; X = O, S, NH, NMe, or CH=CH) and (3; X = O, S, NMe, or CH=CH) from readily available precursors.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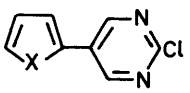
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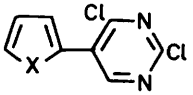
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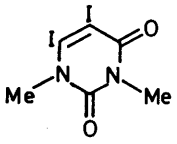
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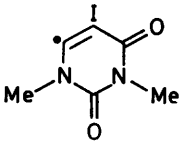
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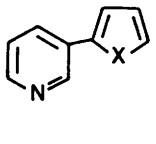
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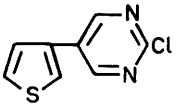
The photolysis of iodoarenes [10-12] and the free radical nature of the reaction [13,14] have been known for some time. However, little attention has been paid to the synthetic utility of the photolysis of iodoheteroarenes. It has been shown that photolysis of 5,6-di-iodo-1,3-dimethyluracil (4) does not lead to the corresponding pyrimidyne but proceeds instead with loss of the iodine at position 6 to give the radical (5). This couples with furan or benzene to give the corresponding 6-(heteroaryl)-1,3-dimethyluracil.[15] The photolysis of 3-iodopyridine in a variety of heteroarenes has been reported [16] to give reasonable yields of the 3-(2-heteroaryl)pyridines (6; X = O, S, NH, or NMe), and we have investigated the possibility of extending this approach to the synthesis of 5-substituted pyrimidines.

We find that photolysis of the readily available 2-chloro-5-iodopyrimidine [17] in a 25% v/v solution of the heteroarene (furan, thiophen, pyrrole, or *N*-methylpyrrole) in acetonitrile gives the 2-chloro-5-heteroarylpyrimidine (2; X = O, S, NH, and NMe) directly in 58—75% yields. Similarly, photolysis of 2-chloro-5-iodopyrimidine in benzene–acetonitrile gives 2-chloro-5-phenylpyrimidine (2; X = CH=CH) in 74% yield. The reactions occur on irradiation of the reaction mixture with either a low- or a medium-pressure mercury arc, the former giving a slightly cleaner product. Work-up is particularly easy: evaporation and recrystallisation from light petroleum affords the product. T.l.c. shows that only in the case of thiophen is a trace of the 3-substituted isomer (7) formed (2% yield).

When 2-chloro-5-(2-thienyl)pyrimidine (2; X = S) was photolysed in acetonitrile, no trace of the 3-isomer (7) was detected even after 48 h irradiation. This contrasts with the photolysis of 2-phenylthiophen (8) which gives the 3-isomer (9) in 40% yield, the reaction proceeding *via* a ' Dewar-thiophen ' intermediate.[18]

Similarly, photolysis of 5-iodopyrimidine in the presence of an excess of furan, thiophen, or *N*-methylpyrrole in acetonitrile gives the 5-heteroarylpyrimidine (1; X = O, S, or NMe) in 46—62% yield. Only in the case of thiophen is a trace of the 3-substituted isomer formed. Photolysis in benzene–acetonitrile gives a 74% yield of 5-phenylpyrimidine. The ease and simplicity of this route to 5-substituted pyrimidines contrasts with the lengthy procedures recently reported for the synthesis of 5-(2-thienyl)pyrimidine,[19] which cannot be applied to the 5-(2-furyl) and 5-(2-pyrrolyl) analogues.[20] Similarly, the previously reported route to 5-phenylpyrimidine is lengthy.[21] 5-Iodopyrimidine is conveniently prepared from the readily available 2-chloro-5-iodopyrimidine by treatment with hydrazine in ethanol to give the 2-hydrazino-derivative (10) (in almost quantitative yield), followed by oxidative removal of the hydrazino-group with silver oxide (based on work by Brown *et al.*[22]), this stage proceeding in 55% yield.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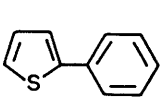
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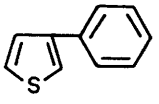
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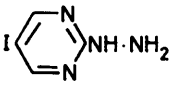
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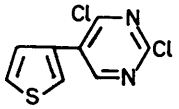
(11)

Photolysis of 2,4-dichloro-5-iodopyrimidine in solutions of furan, thiophen, 1-methylpyrrole, or benzene in acetonitrile gives the 2,4-dichloro-5-(2-heteroaryl-) (or aryl-)pyrimidine (3; X = O, S, NMe, or CH=CH) in 40—60% yield. In the reaction with thiophen, the 3-thienyl isomer (11) may also be isolated in 7% yield. In the reaction with 1-methylpyrrole, five products in addition to the expected product (3; X = NMe) were detected by t.l.c. By column chromatography (on alumina) the main product (3; X = NMe) was obtained pure, together with a small amount of an unstable compound to which we assign structure (12) or (13) on the basis of spectroscopic data. The $^1$H n.m.r. spectrum of this compound (in $CDCl_3$) shows the presence of one pyrimidine ring proton (δ 8.7), six pyrrole ring protons (δ 7.3—6.1), and two *N*-methyl groups (δ 3.8 and 3.4). The mass spectrum shows an apparent molecular ion at

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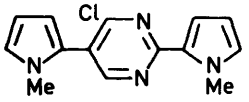
[17] D. J. Brown and D. W. Arantz, *J. Chem. Soc.* (*C*), 1971, 1889.
[18] H. Wynberg and H. van Driel, *J. Amer. Chem. Soc.*, 1965, **87**, 3998.
[19] J. Bourguigon, J. M. Boucly, J.-C. Clinet, and G. Queguiner, *Compt. rend.*, 1975, **281C**, 1019.
[20] D. W. Allen and D. J. Buckland, unpublished observations.
[21] A. Maggiolo and P. B. Russel, *J. Chem. Soc.*, 1951, 3297.
[22] M. E. C. Biffin, D. J. Brown, and T. C. Lee, *J. Chem. Soc.* (*C*), 1967, 573.

*m/e* 272, and indicates the presence of one chlorine atom. Because of the instability of the compound, a satisfactory microanalysis could not be obtained.



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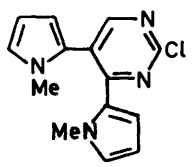

(13)

However, in the photolysis of 2-chloro-5-iodopyrimidine in the presence of 1-methylpyrrole, only the required compound (2; X = NMe) was formed; the range of additional products observed in the photolysis of 2,4-dichloro-5-iodopyrimidine is not observed in this case, suggesting that the above product has structure (13). Support for this assignment comes from the products of photolysis of 4-chloro-5-iodopyrimidine in 1-methylpyrrole–acetonitrile. This reaction gives a mixture of unidentified products in addition to the expected 4-chloro-5-(1-methylpyrrol-2-yl)pyrimidine, which was isolated in only 8% yield. Similarly, low yields (<10%) of 4-chloro-5-(2-furyl)-, 4-chloro-5-(2-thienyl)-, and 4-chloro-5-phenyl-pyrimidine were obtained by photolysis of 4-chloro-5-iodopyrimidine in solutions of furan, thiophen, and benzene, respectively, in acetonitrile. The low yields of these products are attributed to the instability of 4-chloro-5-iodopyrimidine, which decomposes spontaneously.

## EXPERIMENTAL

$^1$H N.m.r. spectra were recorded at 60 MHz with a JEOL C-60 instrument (tetramethylsilane as internal standard). Mass spectra were recorded at 70 eV with an A.E.I. MS30 spectrometer. M.p.s were determined with a Kofler hot-stage apparatus.

*Preparation of Iodopyrimidines.*—2-Chloro-5-iodo- and 2,4-dichloro-5-iodo-pyrimidine were prepared as described previously.[17,23]

*5-Iodopyrimidine.* To a solution of 2-chloro-5-iodopyrimidine (0.012 5 mol) in ethanol (20 cm$^3$) was added hydrazine hydrate (0.012 5 mol) and the solution was heated under reflux for 1 h before being cooled in ice. The resulting solid was filtered off and recrystallised from toluene to give *2-hydrazino-5-iodopyrimidine* (10) (95%), m.p. 196—197° (Found: C, 20.15; H, 2.0; N, 23.7. $C_4H_5IN_4$ requires C, 20.35; H, 2.15; N, 23.75%); *m/e* 236 ($M^+$); δ [$(CD_3)_2SO$] 8.5 (2 H, s), 4.2br (2 H, s) and 3.4br (1 H, s) (signals at δ 4.2 and 3.4 were removed on addition of $D_2O$). A mixture of (10) (0.01 mol) and silver oxide (0.02 mol) was heated under reflux for 2 h in absolute ethanol (40 cm$^3$), filtered hot, and evaporated under reduced pressure. The residue was purified by vacuum sublimation (60 °C and 0.2 mmHg) to yield *5-iodopyrimidine* (1.13 g, 55%), m.p. 126° (with sublimation) (Found: C, 23.05; H, 1.1; N, 13.25. $C_4H_3IN_2$ requires C, 23.3; H, 1.45; N, 13.6%); *m/e* 206 ($M^+$); δ($CDCl_3$) 9.25 (1 H, s) and 9.1 (2 H, s).

*4-Chloro-5-iodopyrimidine.* Vacuum-dried 5-iodopyrimidin-4-one[24] (0.01 mol) was added to a mixture of phosphoryl chloride (5 cm$^3$) and *NN*-dimethylaniline (0.5 cm$^3$), and the resulting mixture was heated under reflux for 1 h. The excess of phosphoryl chloride was removed under reduced pressure, and the residue added to ice. The resulting emulsion was extracted with ether (4 × 10 cm$^3$) and the extract washed with sodium disulphite solution followed by water, dried ($MgSO_4$), and evaporated. The residue was purified by vacuum sublimation to give *4-chloro-5-iodopyrimidine* (1.18 g, 49%), m.p. 61—62° (Found: C, 20.1; H, 1.15; N, 11.35. $C_4H_2ClIN_2$ requires C, 20.0; H, 0.85; N, 11.65%); *m/e* 240 ($M^+$); δ($CDCl_3$) 9.25 (1 H, s) and 8.9 (1 H, s).

*Photolysis of 2-Chloro-5-iodopyrimidine.*—A solution of 2-chloro-5-iodopyrimidine (0.005 mol) in the appropriate heteroarene or benzene (25 cm$^3$) was diluted with acetonitrile (75 cm$^3$) and irradiated with a low-pressure Hanovia mercury arc (quartz filter) until all traces of the iodopyrimidine had disappeared (t.l.c. on alumina) (*ca.* 10 h). The solvent was then removed under reduced pressure, and the residue extracted with and recrystallised from light petroleum (b.p. 40—60 °C) to give *2-chloro-5-(2-furyl)pyrimidine* (2; X = O) (0.68 g, 75%), m.p. 135° (Found: C, 53.0; H, 2.75; N, 15.4. $C_8H_5ClN_2O$ requires C, 53.2; H, 2.8; N, 15.5%); *m/e* 180 ($M^+$); δ($CDCl_3$) 8.7 (2 H, s), 7.6 (1 H, d), 6.7 (1 H, d), and 6.4 (1 H, m).

*2-Chloro-5-(2-thienyl)pyrimidine* (2; X = S) (0.57 g, 58%) had m.p. 123° (Found: C, 48.8; H, 2.5; N, 13.7. $C_8H_5ClN_2S$ requires C, 48.85; H, 2.55; N, 14.25%); *m/e* 196 ($M^+$); δ($CDCl_3$) 8.9 (2 H, s) and 7.5 (3 H, m).

Column chromatography [Alumina type H; $CHCl_3$–light petroleum (b.p. 40—60 °C), 7½ : 92½ v/v] of the mixture obtained from irradiation of 2-chloro-5-iodopyrimidine in thiophen–acetonitrile also gave *2-chloro-5-(3-thienyl)pyrimidine* (7) (0.02 g, 2%), m.p. 146° (Found: C, 48.7; H, 2.45; N, 13.85. $C_8H_5ClN_2S$ requires C, 48.85; H, 2.55; N, 14.25%); *m/e* 196 ($M^+$); δ($CDCl_3$) 8.6 (2 H, s) and 7.3 (3 H, m).

*2-Chloro-5-(2-pyrrolyl)pyrimidine* (2; X = NH) (0.44 g, (49%) had m.p. 137—138° (decomp.) (Found: C, 53.85; H, 3.45; N, 23.45. $C_8H_6ClN_3$ requires C, 53.5; H, 3.35; N, 23.4%); *m/e* 179 ($M^+$); δ($CDCl_3$) 8.85 (2 H, s), 8.75 (1 H, s), 6.9 (1 H, m) and 6.3 (2 H, m).

*2-Chloro-5-(1-methylpyrrol-2-yl)pyrimidine* (2; X = NMe) (58%) had m.p. 125° (Found: C, 55.8; H, 4.2; N, 21.75. $C_9H_8ClN_3$ requires C, 55.85; H, 4.15; N, 21.7%); *m/e* 193 ($M^+$); δ($CDCl_3$) 8.7 (2 H, s), 7.3 (1 H, m), 6.85 (2 H, m), and 3.3 (3 H, s).

2-Chloro-5-phenylpyrimidine (2; X = CH=CH) (0.71 g, 74%) had m.p. 123° (lit.,[25] 122—124°).

*Photolysis of 5-Iodopyrimidine.*—The above procedure was repeated with 5-iodopyrimidine (0.005 mol) to give *5-(2-furyl)pyrimidine* (1; X = O) (0.45 g, 62%), m.p. 57° (Found: C, 65.45; H, 4.05; N, 19.35. $C_8H_6N_2O$ requires C, 65.75; H, 4.15; N, 19.15%); *m/e* 146 ($M^+$); δ($CDCl_3$) 8.95 (1 H, s), 8.9 (2 H, s), 7.5 (1 H, s), 6.7 (1 H, m), and 6.5 (1 H, m); 5-(2-thienyl)pyrimidine (1; X = S) (0.47 g, 58%), m.p. 75° (lit.,[19] 76°) (Found: C, 58.75; H, 3.85; N, 17.4. Calc. for $C_8H_6N_2S$: C, 59.2; H, 3.7; N, 17.3%); *m/e* 162 ($M^+$); δ($CDCl_3$) 8.90 (1 H, s), 8.72 (2 H, s), 7.3 (2 H, m), and 7.0 (1 H, m) [column chromatography (Alumina type H) also gave 5-(3-thienyl)pyrimidine (0.05 g, 6%), m.p. 61° (lit.,[19] 61°)]; *5-(1-methylpyrrol-2-yl)pyrimidine*

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(1; X = NMe) (0.36 g, 46%), m.p. 143—144° (Found: C, 67.55; H, 5.6; N, 26.85. $C_9H_9N_3$ requires C, 67.9; H, 5.7; N, 26.4%); *m/e* 159 ($M^+$); δ($CDCl_3$) 8.94 (1 H, s), 8.64 (2 H, s), 6.68 (1 H, m), 6.2 (2 H, m), and 3.6 (3 H, s); 5-phenylpyrimidine (1; X = CH=CH) (0.58 g, 74%), m.p. 38° (lit.,[21] 25°) (Found: C, 76.8; H, 5.15; N, 18.05. Calc. for $C_{10}H_8N_2$: C, 76.9; H, 5.15; N, 17.95%); *m/e* 156 ($M^+$); δ($CDCl_3$) 8.98 (1 H, s), 8.70 (2 H, s), and 7.30 (5 H, s).

*Photolysis of* 2,4-*Dichloro*-5-*iodopyrimidine*.—The above procedure was repeated with 2,4-dichloro-5-iodopyrimidine (0.005 mol) to give 2,4-*dichloro*-5-(2-*furyl*)*pyrimidine* (3; X = O) (0.6 g, 56%), m.p. 66° (Found: C, 44.45; H, 1.75; N, 12.9. $C_8H_4Cl_2N_2O$ requires C, 44.7; H, 1.9; N, 13.0%); *m/e* 214 ($M^+$); δ($CDCl_3$) 9.25 (1 H, s), 7.8 (1 H, m), 7.4 (1 H, m), and 6.7 (1 H, m); 2,4-*dichloro*-5-(2-*thienyl*)*pyrimidine* (3; X = S) (0.72 g, 62%), m.p. 81—82° (Found: C, 41.4; H, 1.8; N, 12.0. $C_8H_4Cl_2N_2S$ requires C, 41.6; H, 1.75; N, 12.1%); *m/e* 230 ($M^+$); δ($CDCl_3$) 8.9 (1 H, s), 7.7 (2 H, m), and 7.4 (1 H, m) [column chromatography on alumina also gave 2,4-*dichloro*-5-(3-*thienyl*)*pyrimidine* (11) (0.08 g, 7%), m.p. 73° (Found: C, 41.35; H, 1.85; N, 11.95. $C_8H_4Cl_2N_2S$ requires C, 41.6; H, 1.75; N, 12.1%); *m/e* 230 ($M^+$); δ($CDCl_3$) 8.65 (1 H, s) and 7.6—7.1 (3 H, m)]; 2,4-*dichloro*-5-(1-*methylpyrrol*-2-*yl*)*pyrimidine* (3; X = NMe) (0.45 g, 39%); m.p. 59—60° (Found: C, 47.2; H, 2.85; N, 18.2. $C_9H_7Cl_2N_3$ requires C, 47.4; H, 3.1; N, 18.4%); *m/e* 227 ($M^+$); δ($CDCl_3$) 8.4 (1 H, s), 6.8 (1 H, m), 6.2 (2 H, m), and 3.55 (3 H, s) [column chromatography on alumina also gave an unstable compound, *m/e* 272 ($M^+$); δ($CDCl_3$) 8.7 (1 H, s), 7.3—6.1 (6 H, m), 3.8 (3 H, s), and 3.4 (3 H, s), tentatively identified as 2-chloro-4,5-bis-(1-methylpyrrol-2-yl)pyrimidine (13)]; 2,4-dichloro-5-phenylpyrimidine (3; X = CH=CH) (0.55 g, 49%), m.p. 81° (lit.,[26] 78—80°).

*Photolysis of* 4-*Chloro*-5-*iodopyrimidine*.—The above procedure was repeated with 4-chloro-5-iodopyrimidine to give 4-*chloro*-5-(2-*furyl*)*pyrimidine* (0.13 g, 14%), m.p. 83° (Found: C, 52.95; H, 2.65; N, 15.4. $C_8H_5ClN_2O$ requires C, 53.2; H, 2.8; N, 15.5%); *m/e* 180 ($M^+$); δ($CDCl_3$) 8.9 (1 H, s), 8.65 (1 H, s), 7.7 (1 H, m), and 7.4 (2 H, m); 4-chloro-5-(2-thienyl)pyrimidine (0.1 g, 10%), m.p. 56° (lit.,[19] 55°) (Found: C, 48.9; H, 2.6; N, 14.05. Calc. for $C_8H_5ClN_2S$: C, 48.85; H, 2.55; N, 14.25%); *m/e* 196 ($M^+$); δ($CDCl_3$) 9.17 (1 H, s), 8.27 (1 H, s), 7.9 (1 H, d), 7.65 (1 H, m), and 7.42 (1 H, m); 4-*chloro*-5-(1-*methylpyrrol*-2-*yl*)*pyrimidine* (0.08 g, 8%), m.p. 93° (Found: C, 55.6; H, 4.25; N, 21.85. $C_9H_8ClN_3$ requires C, 55.85; H, 4.15; N, 21.7%); *m/e* 193 ($M^+$); δ($CDCl_3$) 8.6 (1 H, s), 8.4 (1 H, s), 6.7 (1 H, m), 6.1 (2 H, m), and 3.8 (3 H, s); 4-chloro-5-phenylpyrimidine (0.15 g, 16%), m.p. 72° (lit.,[26] 71—72°).

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[26] W. H. Davies and H. A. Piggott, *J. Chem. Soc.*, 1945, 347.