Heterocyclic Transformations. Part 5:[1] Studies in Reactions of 6-Methyl-1,3-oxazine-2,4(3*H*)-dione with Arylamines—a Facile Synthesis of 1-Aryl-6-methyluracils

Harjit Singh, Palwinder Singh, Pawan Aggarwal and Subodh Kumar
Department of Chemistry, Guru Nanak Dev University, Amritsar-143 005, India

6-Methyl-1,3-oxazine-2,4(3*H*)-dione **1** reacts with 2 equiv. arylamines **3** at 150–160 °C to give 1-aryl-6-methyluracils **5** or 1-aryl-3-(3-aryliminobutanoyl)ureas **4**. The latter—as well as mixtures of **1** and **3** (2 equiv.) on refluxing, in isopentanol in some cases or in acetic acid in general—provide a facile synthesis of **5**. The role of the stoichiometric excess of arylamines as against an equiv. of an alkylamine in similar reactions has been rationalized.

Substituted uracil derivatives preeminent for their biological activity[2] are constituents of modified nucleic acids[3] and also provide useful biochemical diagnostic probes[4] and potential synthons.[5] Monosubstitution reactions at nitrogen of uracil are plagued by N-1, N-3 and *N,O*-disubstitutions.[6,7] N-1 alkylations in uracil[8] and N-3 alkylations in 6-aminouracil[9] have been beneficially performed with their silylated derivatives using iodine as catalyst but arylation reactions do not take place. In an alternative approach, 1-alkyl-6-methyluracils have been obtained in facile manner by reactions of alkylamines[10–14] with 6-methyl-1,3-oxazine-2,4(3*H*)-diones, but similar reactions with arylamines are not reported. Here we have studied various aspects of the reactions of 6-methyl-1,3-oxazine-2,4(3*H*)-dione **1** with arylamines and have found that their 1:2 stoichiometric reactions—(i) in refluxing acetic acid, or (ii) on heating (150–160 °C) followed by acetic acid refluxing—constitute optimal synthetic methodologies for procuring 1-aryl-6-methyluracils **5**. The role of the intermediacy of 1-aryl-3-(3-aryliminobutanoyl)-ureas **4** against that of 3-acetoacetyl-1-phenylureas as intermediates in the reactions of alkylamines, rationalizes the use of a stoichiometric excess of arylamines in these reactions.

Dione **1** with aniline in refluxing acetonitrile or ethanol containing triethylamine (2 equiv.)* gave phenylurea (70%), m.p. 145 °C (lit.,[15] m.p. 147 °C) and 3-acetyl-1-phenylurea (20%), m.p. 183 °C (lit.,[16] m.p. 183 °C). Evidently, aniline reacts at C-2 of **1** to form 3-acetoacetyl-1-phenylurea **2** (X = H), which due to the weaker basic nature of N-1 does not cyclize, but undergoes triethylamine induced deacetylation (path a) and deacetoacetylation (path b) (Scheme 1) to form 3-acetyl-1-phenylurea and phenylurea, respectively.

On heating a mixture of dione **1** and aniline (1 equiv.) at 150–160 °C, a white solid formed [*m/z* 295 (M^+)] which from its spectral data [δ_H 3.95 (CH_2) and 6.0 (5-H)] has been found to be a 3:7 mixture of imine (**X**) and enamine (**Y**) tautomers of urea derivative **4a**. In this reaction 40% of **1** was recovered unchanged. Furthermore, **1** with aniline (2 equiv.) gave 6-methyl-1-phenyl-1*H*-uracil **5a** in excellent yield (90%). The compound **4a** was quite stable to heating (150–160 °C), but when heated after adding a drop of aniline, it cyclized to **5a** quantitatively. In another experiment **1** with 1.7 equiv. of aniline gave compound **4a** in 80% yield. Therefore, **1** with 2 equiv. or more of aniline gave the uracil **5a**, but with lesser amounts of aniline, reaction terminated at the intermediate **4** stage. Similarly, **1** on refluxing with 2 equiv. of 3-hydroxy-, 4-hydroxy-, 3-methoxy- and 4-methyl-anilines gave the respective uracils **5c, d, k, i** (Table 1). But, **1** with 2-hydroxy-, 2-methyl-, 3-methyl-, 2-methoxy- and 4-chloro-anilines gave intermediates **4b, g, h, j, m**, respectively (Table 2) which existed only in enamine tautomeric form **Y** [δ_H 5.5–6.0 (=CH) present, 4.0–4.5 ($-CH_2$) absent]. The dry heating (150–160 °C) of **1** with 4-methoxyaniline gave product **4l**, which existed in imine form **X**, but on further heating (170–180 °C) tautomerized to enamine **Y**. However, **1** on heating with **3e** and **f** gave some unidentifiable products. The UV spectra of the compounds **4** which exist in enamine form, show λ_{max}/nm 270 ± 10 and those which exist in imine form, show λ_{max}/nm 315 ± 10. The compounds **4** which are mixtures of imine and enamine tautomers (^{1}H NMR) show λ_{max}/nm 270 ± 10 and 315 ± 10. Therefore UV spectra can qualitatively define the presence or absence of tautomers in compounds **4**, but only ^{1}H NMR can provide their quantitative essay.

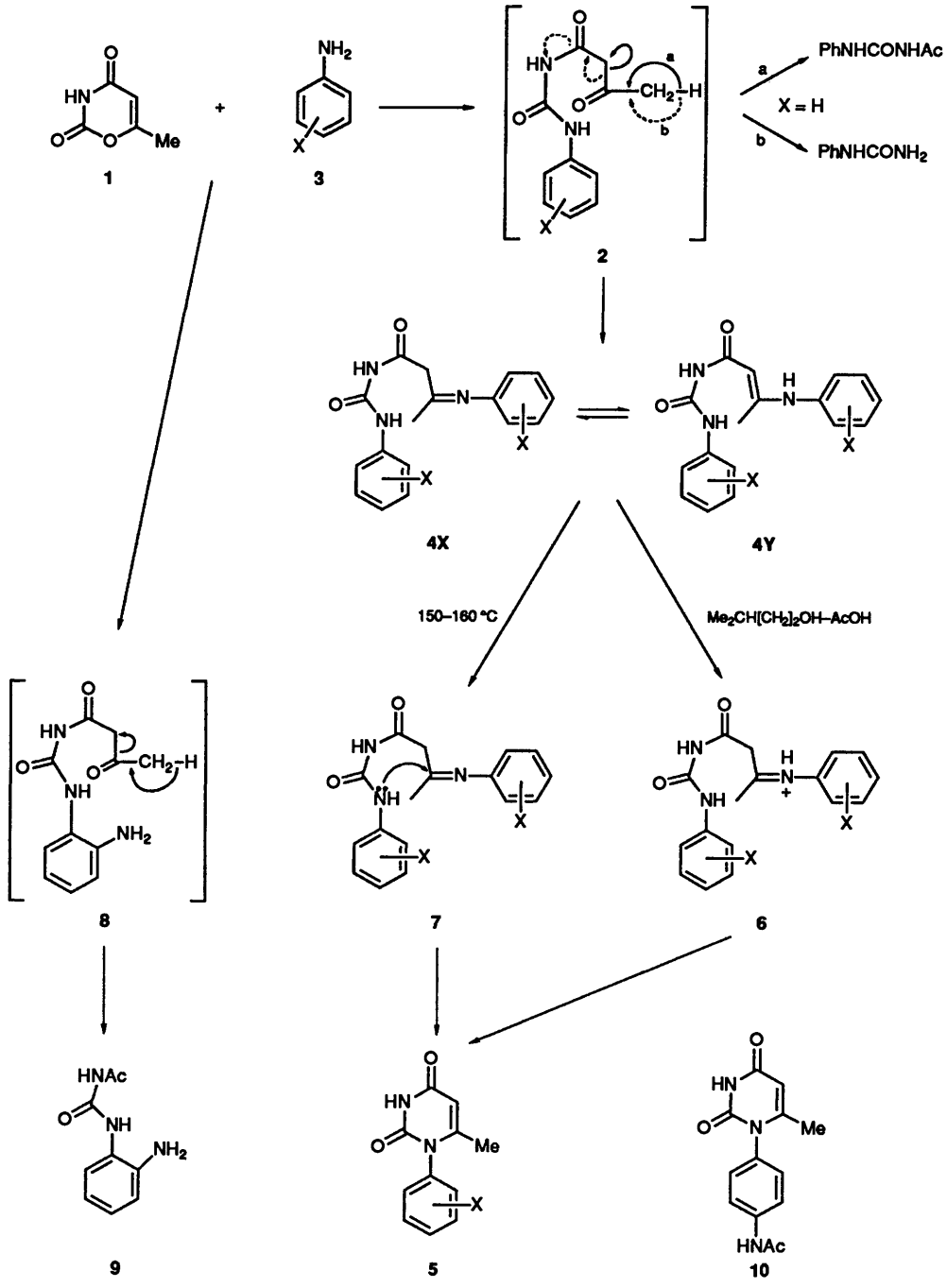
It may be noted that **1** with arylamine (2 equiv.) at 150–160 °C gave corresponding uracils **5** in some cases, whereas in others the reactions stopped at intermediate stage. In all the latter cases, the intermediates had enamine structures.

It was envisaged that in the presence of an alcohol or acid, the intermediates **4** could be protonated to form iminium cations, which would undergo facile cyclization to the respective uracils **5**. Compounds **4b** (2-OH), **4h** (3-Me) and **4l** (4-OMe) on refluxing in isopentanol cyclized to their respective uracils **5b, h, l**. However, **4g** (2-Me), **4j** (2-OMe) and **4m** (4-Cl), derivatives did not cyclize even on prolonged refluxing (24 h) in isopentanol. In a single operation procedure, **1** and arylamines (2 equiv.) **3a, b** (2-OH), **3c** (3-OH), **3d** (4-OH), **3f** (4-NH), **3h** (3-Me), **3i** (4-Me), **3k** (3-OMe), **4l** (4-OMe) on refluxing in isopentanol† gave the uracils **5** (Table 1). In these reactions, except in case of **3b** and **d**, the termination of the reactions after 2 h provided the respective compounds **4** in 70–80% yields. However, **1** with 2-aminoaniline gave 3-acetyl-1-(2-aminophenyl)-urea **9**, which might be formed by the facile intramolecular deacetylation induced by the *ortho*-amino group in intermediate 3-acetoacetyl-1-phenylurea **8**. Dione **1** with arylamines **3g, j, m**, gave only compounds **4g, j, m** respectively which remained unchanged on further refluxing. The ^{1}H NMR spectra of compounds **4** formed by refluxing **1** with arylamines in isopentanol show them to exist as mixtures of imine and enamine tautomers or as pure imine tautomer, which is contrary to the results obtained in dry heating reactions, where compounds **4** exist in enamine form.

In the above reactions, it could be visualised that initially formed acetoacetyl-1-arylureas **2** react with another molecule of arylamine to give compounds **4**, existing as imine and/or enamine tautomers. The compounds **4** undergo protonation in isopentanol to iminium cations **6**, which cyclize to give the

* In the absence of triethylamine the reaction failed in refluxing acetonitrile, xylene or DMF, even with an excess of arylamine.

† **1** with arylamines (1 equiv.) in isopentanol gave isopentyl *N*-acetoacetylcarbamate (50–60%).[18]



3–7; a, X = H; b, X = 2–OH; c, X = 3–OH; d, X = 4–OH; f, X = 4–NH_2; g, X = 2–Me; h, X = 3–Me; I, X = 4–Me; j, X = 2–OMe; k, X = 3–OMe; l, X = 4–OMe; m, X = 4–Cl.

Scheme 1

respective uracils **5**. However, in reactions of **1** with alkylamines only 1 equiv. of alkylamine is required.[18] Evidently in the case of alkylamines the more basic urea N-1 of analogues of **2** reacts at C=O to form the uracils, but in the case of arylamines due to lower basicity of N-1 in **2**, it does not react at C=O group, and attacks at the more reactive C=N of the imine derivative **4**. In compounds **4g** and **j** the steric hindrance due to *ortho*-substituents and in **4m** the lowered basicity of N-1, could inhibit the attack of N-1 at C=N unit and cause the termination of the reaction at intermediate stage.

The compounds **4g**, **j**, **m** which did not cyclize in isopentanol, underwent cyclization on refluxing in acetic acid to give compounds **5g**, **j**, **m**, respectively (Table 1). Similarly, other compounds **4** also cyclized in acetic acid to give compounds **5** in higher yields than in isopentanol. However **4f** on refluxing in acetic acid gave a product [m.p. 280 °C, *m/z* 259 (M^+)] which from the appearance of two 1.5 H additional signals, not expected in ^1H NMR of aryluracils **5f**, could be assigned the structure **10** where $-NH{=}{=}{=}C(Me){=}{=}{=}O$ due to restricted rotation splits the Me signal into two. Further, **1** and arylamines **3** on refluxing in acetic acid gave compounds **5**, but in lower yields than achieved in the case of dry heating or followed by refluxing in acetic acid (Table 3).

Similarly, the compounds **4** on heating in PPA gave compounds **5** but in quite low yields. The heating of **1** and arylamines in PPA did not provide compounds **5**. Therefore in acetic acid and PPA the ease in protonation of enamine or imine tautomers of **4** to form iminium cations facilitates the cycliz-

Table 1 Physical and spectral data of uracils **5** and **10**

Compound[a]	M.p.[b]/°C	δ_H	δ_C($CDCl_3$ + [$^2H_6$]DMSO)	*m/z* (%)	ν_{max}(KBr)/cm^{-1}	λ_{max}(EtOH)/nm, ($10^4\varepsilon$)
5a	280 (lit.,[17] 280)	($CDCl_3$ + TFA) 2.00 (3 H, s, 6-Me), 6.00 (1 H, s, 5-H), 7.00–7.50 (5 H, m, ArH)	20.39 (q, Me), 100.94 (d, C-5), 128.75 (d, ArCH), 129.24 (d, ArCH), 136.49 (s, ArC-1), 151.32, 153.47 (s, C-2, C-6), 162.83 (s, C-4)	202 (100), 144 (34), 131(22), 118 (24)	1700, 1660	263.5 (1.21)
5b	302	($CDCl_3$ + [$^2H_6$]DMSO) 1.75 (3 H, s, 6-Me), 5.60 (1 H, s, 5-H), 6.85–7.30 (4 H, m, ArH), 10.00 (1 H, br, NH, exch. D_2O), 11.25 (1 H, br, exch. D_2O)	19.52 (q, Me), 100.54 (d, C-5), 116.62 (d, ArCH), 119.41 (d, ArCH), 123.68 (s, ArC-1), 130.21 (d, ArCH), 130.32 (d, ArCH), 151.04 (s, ArC), 153.37, 154.47 (s, C-2, C-6), 163.00 (s, C-4)	218	1720, 1670	265.9 (1.17)
5c	270	($CDCl_3$ + TFA) 2.05 (3 H, s, 6-Me), 6.00 (1 H, s, 5-H), 6.60–7.50 (4 H, m, ArH)	18.44 (q, Me), 99.01 (d, C-5), 114.01 (d, ArCH), 114.17 (d, ArCH), 117.34 (d, ArCH), 128.13 (d, ArCH), 135.62 (s, ArC-1), 149.47 (s, ArC-3), 152.01, 156.34 (s, C-2, C-6), 161.10 (s, C-4)	218 (84), 175 (11), 160 (12), 147 (100)	1720, 1680	265.5 (1.17)
5d	330	($CDCl_3$ + TFA) 2.00 (3 H, s, 6-Me), 6.05 (1 H, s, 5-H), 7.0 (4 H, m, ArH)	($CDCl_3$ + DMF) 20.85 (q, CH_3), 101.20 (d, C-5), 116.26 (d, ArC-3), 128.36, 130.10 (d, ArC-2), 152.24, 154.95, 158.52 (s, C-2, ArC-4, C-6), 163.47 (s, C-4)	218 (100), 175 (81), 160 (42), 145 (21), 133 (34)	1700, 1660	265.9 (1.29)
5f	266–268	($CDCl_3$ + TFA) 2.00 (3 H, s, 6-Me), 6.00 (1 H, s, 5-H), 7.78–7.90 (4 H, m, ArH)	19.52 (q, Me), 99.90 (d, C-5), 115.59 (d, ArCH), 127.91 (d, ArCH), 143.74 (s, ArCN), 150.64, 153.08 (s, C-2, C-6), 161.96 (s, C-4)	217 (100), 173 (48), 145 (22), 123 (40)	1690, 1650	262.7 (1.34)
5g	180–182	($CDCl_3$ + [$^2H_6$]DMSO) 1.78 (3 H, s, 6-Me), 2.16 (3 H, s, ArMe), 5.64 (1 H, s, 5-H), 7.14–7.35 (4 H, m, ArH), 9.00 (1 H, br, NH, exch. D_2O)	16.16 (q, Me), 19.53 (q, Me), 100.84 (d, C-5), 127.40 (d, ArCH), 128.16 (d, ArCH), 128.61 (d, ArCH), 131.31 (d, ArCH), 134.58 (s, ArC), 135.22 (s, ArC), 150.27, 152.52 (s, C-2, C-6), 162.53 (s, C-4)	216 (100), 173 (80), 158 (37), 132 (30), 91 (25)	1720, 1680	260.3 (1.01)
5h	215–217	($CDCl_3$ + [$^2H_6$]DMSO) 1.85 (3 H, s, 6-Me), 2.38 (3 H, s, ArMe), 5.64 (1 H, s, 5-H), 6.99–7.40 (4 H, m, ArH), 10.62 (1 H, br, NH, exch. D_2O)	20.53 (q, Me), 20.75 (q, Me), 101.25 (d, C-5), 125.03 (d, ArCH), 128.57 (d, ArCH), 129.03 (d, ArCH), 129.66 (d, ArCH), 135.75 (s, ArC), 139.36 (s, ArC), 151.33, 153.50, (s, C-2, C-6), 163.06 (s, C-4)	216 (100), 173 (54), 158 (39), 145 (42), 132 (25)	1752, 1696	263.7 (1.30)
5i	280–282	($CDCl_3$ + [$^2H_6$]DMSO) 1.84 (3 H, s, 6-Me), 2.37 (3 H, s, ArMe), 5.63 (1 H, s, 5-H), 7.07 (2 H, d, *J* 7 Hz, ArH), 7.26 (2 H, d, *J* 7 Hz, ArH), 8.73 (1 H, br, NH, exch. D_2O)	19.01 (q, Me), 19.25 (q, Me), 99.59 (d, C-5), 126.76 (d, ArCH), 128.29 (d, ArCH), 132.36 (s, ArC), 136.95 (s, ArC), 149.96, 151.89 (s, C-2, C-6), 161.29 (s, C-4)	216 (56), 195 (100), 173 (43), 158 (27), 132 (20)	1720, 1669	244.3 (2.15)
5j	205–207	($CDCl_3$ + [$^2H_2$]DMSO) 1.79 (3 H, s, 6-Me), 3.83 (3 H, s, OMe), 5.56 (1 H, s, 5-H), 7.01–7.88 (4 H, m, ArH), 11.24 (1 H, br, NH, exch. D_2O)	19.32 (q, Me), 54.09 (q, OMe), 100.20 (d, C-5), 113.18 (d, ArCH), 113.52 (d, ArCH), 119.45 (d, ArCH), 128.87 (d, ArCH), 136.29 (s, ArCN), 150.29, 152.06, 159.01 (s, C-2, C-6, ArC), 161.83 (s, C-4)	232 (100), 195 (22), 189 (26), 174 (16), 164 (75), 123 (25)	1710, 1680	260.5 (1.84)
5k	98–100	($CDCl_3$ + [$^2H_6$]DMSO) 1.87 (3 H, s, 6-Me), 3.82 (3 H, s, OMe), 5.57 (1 H, s, 5-H), 6.80–7.79 (4 H, m, ArH), 11.24 (1 H, s, NH, exch. D_2O)	19.32 (q, Me), 54.09 (q, Me), 100.20 (d, C-5), 113.18 (d, ArCH), 113.52 (d, ArCH), 119.45 (d, ArCH), 128.87 (d, ArCH), 136.29 (s, ArC), 150.29, 152.06, 159.01 (s, C-2, ArC, C-6), 161.83 (s, C-4)	232 (100), 195 (22), 189 (26), 146 (75), 123 (25)	1710, 1680	260.5 (1.84)
5l	270	($CDCl_3$ + TFA) 1.88 (3 H, s, 6-Me), 3.84 (3 H, s, OMe), 5.67 (1 H, s, 5-H), 6.90 (4 H, s, ArH), 6.98 (2 H, d, *J* 6 Hz, ArH), 7.14 (d, 2 H, *J* 6 Hz, ArH)	18.88 (q, Me), 53.60 (q, OMe), 99.36 (d, C-5), 112.76 (d, ArCH), 127.39 (s, ArCN), 128.07 (d, ArCH), 149.49 (s, ArCOMe), 152.19, 157.67 (s, C-6/C-2), 161.16 (s, C-4)	232 (100), 190 (81), 175 (57), 123 (11)	1720, 1680	265.1 (1.52)
5m	310	($CDCl_3$ + TFA) 2.00 (3 H, s, 6-Me), 5.99 (1 H, s, 5-H), 7.18–7.56 (4 H, m, ArH)	21.03 (q, Me), 101.58 (d, C-5), 129.55 (d, ArCH), 130.43 (d, ArCH), 133.61 (s, ArC), 136.37 (s, ArC), 151.83, 156.71 (s, C-6, C-2), 165.36 (s, C-4)	238 (25), 236 (73), 195 (35), 193 (100), 180 (26), 152 (78)	1720, 1672	262.7 (1.54)
10	280	($CDCl_3$ + [$^2H_6$]DMSO) 1.84 (3 H, s, Me), 2.06 (1.5 H, s, CO), 2.12 (1.5 H, s, COMe), 5.53 (1 H, s, 5-H), 7.13–7.95 (4 H, m, ArH)	19.69 (q, Me), 22.84 (q, Me), 100.33 (d, C-5), 118.08 (d, ArCH), 127.20 (d, ArCH), 129.35 (d, ArCH), 132.83 (s, ArC), 139.89 (s, ArC), 149.93, 152.96 (s, C-2, C-6), 171.81 (s, C-4), 167.40 (s, COMe)	259 (4), 217 (17), 192 (69), 150 (43), 108 (100)	1720, 1704, 1672	264.1 (1.68)

[a] Elemental analyses: **5a** (Found: C, 65.5; H, 4.1; N, 13.9. $C_{11}H_{10}N_2O_2$ requires C, 65.34; H, 4.31; N, 13.86%); **5b** (Found: C, 60.3; H, 4.6; N, 12.9. $C_{11}H_{10}N_2O_3$ requires C, 60.55; H, 4.58; N, 12.84%); **5c** (Found: C, 60.4; H, 4.6; N, 12.9. $C_{11}H_{10}N_2O_3$ requires C, 60.55; H, 4.58; N, 12.84%); **5d** (Found: C, 60.4; H, 4.6; N, 12.7. $C_{11}H_{10}N_2O_3$ requires C, 60.55; 4.58; N, 12.84%); **5f** (Found: C, 59.9; H, 4.9; N, 19.1. $C_{11}H_{11}N_3O_2$ requires C, 60.7; H, 5.07; N, 19.3%); **5g** (Found: C, 66.5; H, 4.5; N, 12.5. $C_{12}H_{12}N_2O_2$ requires C, 66.66; H, 5.55; N, 12.96%); **5h** (Found: C, 66.9 H, 5.4; N, 12.6. $C_{12}H_{12}N_2O_2$ requires C, 66.66; H, 5.55; N, 12.96%); **5i** (Found: C, 67.1; H, 5.4; N, 12.5. $C_{12}H_{12}N_2O_2$ requires C, 66.66; H, 5.55; N, 12.96%); **5j** (Found: C, 62.4; H, 4.9; N, 11.8. $C_{12}H_{12}N_2O_3$ requires C, 62.06; H, 5.19; N, 12.06%); **5k** (Found: C, 61.6; H, 4.9; N, 11.9. $C_{12}H_{12}N_2O_3$ requires C, 62.06; H, 5.19; N, 12.06%); **5l** (Found: C, 62.0; H, 5.2; N, 12.2. $C_{12}H_{12}N_2O_3$ requires C, 62.06; H, 5.17; N, 12.06%); **5m** (Found: C, 55.6; H, 3.5; N, 11.3. $C_{11}H_9N_2O_2Cl$ requires C, 55.81; H, 3.80; N, 11.83%); **10** (Found: C, 60.6; H, 5.6; N, 15.9. $C_{13}H_{13}N_3O_3$ requires C, 60.23; H, 5.01; N, 16.21%). [b] Solvent of crystallization: methanol–ether.

Table 2 Physical and spectral data of compounds **4**

Compound[a]	M.p.[b]/°C	Yield (%)	δ_H	*m/z* (%)	ν_{max}(KBr)/cm^{-1}	λ_{max}(EtOH)/nm (10^4 ε)
4a	215–218	80	($CDCl_3$ + [$^2H_6$]DMSO) 2.05 (8/10 × 3 H, s, Me), 2.50 (1/10 × 3 H, s, Me), 2.70 (1/10 × 3 H, s, Me), 3.95 (1/10 × 2 H, s, CH_2), 6.00 (1/10 × H, s, =CH), 6.20 (8/10 × H, s, =CH), 7.15–7.80 (m, ArH)	295 (7), 202 (100), 159 (51), 144 (40), 118 (36)	1700, 1680	318 (1.31), 261 (1.37)
4b	250	88	($CDCl_3$ + TFA) 2.25 (3 H, s, Me), 6.0 (1 H, s, =CH), 7.20 (8 H, m, ArH)	327	1770, 1740, 1690	279 (1.04), 225 (1.41)
4c	202–205	85	($CDCl_3$ + TFA) 2.15 (3/10 × 3 H, s, Me), 2.45 (7/10 × 3 H, s, Me), 3.95 (7/10 × 2 H, s, CH_2), 6.20 (3/10 × 1 H, s, =CH), 6.90–7.50 (8 H, m, ArH)	327 (1), 219 (50), 176 (21), 148 (59), 110 (100), 81 (25)	1680, 1654	319. (1.10), 235 (0.48)
4f	260–263	60	($CDCl_3$ + TFA) 2.00 (3/10 × 3 H, s, Me), 2.36 (7/10 × 3 H, s, Me), 4.00 (2 H, s, CH_2), 6.00 (1 H, s, =CH), 7.33–7.60 (m, ArH)	340	1770, 1724	317 (1.21), 240 (1.01)
4g	203	62	($CDCl_3$) 1.87 (3 H, s, Me), 2.30 (3 H, s, ArMe), 2.35 (3 H, s, ArMe), 4.83 (1 H, s, =CH), 7.01–7.24 (7 H, m, ArH), 8.11 (1 H, d, *J* 8 Hz, ArH), 9.09 (1 H, s, NH, exch. D_2O), 10.75 (1 H, s, NH, exch. D_2O), 10.94 (1 H, s, NH, exch. D_2O)	339	1704, 1640, 1608	248.7 (3.03), 216 (1.65)
4h	167	65	($CDCl_3$) 2.02 (3 H, s, Me), 2.34 (3 H, s, ArMe), 2.35 (3 H, s, ArMe), 4.81 (1 H, =CH), 6.87–7.45 (8 H, m, ArH), 9.16 (1 H, s, NH, exch. D_2O), 10.90 (1 H, s, NH, exch. D_2O), 10.92 (1 H, s, NH, exch. D_2O)	339	1704, 1640, 1608	260.9 (2.82), 215 (1.61)
4j	227	80	($CDCl_3$ + TFA) 1.82 (4/10 × 3 H, s, Me), 2.03 (6/10 × 3 H, s, Me), 3.75 (12 H, s, 4 × Me), 5.74 (2 H, s, =CH), 6.83–7.82 (16 H, m, ArH)	355	1704, 1640, 1600	264.3 (2.77)
4l(X)	184	92	($CDCl_3$ + TFA) 2.0 (3 H, s, Me), 3.90 (8 H, s, CH_2 and 2 × OCH_3), 6.85–7.40 (8 H, m, ArH)	355 2.5), 312 (1.5), 233 (48), 189 (59), 174 (36), 123 (100)	1700	316.9 (1.75), 231.7 (1.74)
4l(Y)	210	91	($CDCl_3$ + TFA) 2.0 (3 H, s, Me), 3.80 (6 H, s, 2 × Me), 5.90 (1 H, s, =CH), 6.75–7.10 (8 H, m, ArH)	355 (2.5), 312 (1.5), 233 (48), 189 (59), 174 (36), 123 (100)	1720, 1680	260.3 (1.03), 280.5 (0.77)
4m	257	75	($CDCl_3$ + TFA) 2.26 (3 H, s, Me), 4.18 (1 H, s, =CH), 7.18–7.66 (8 H, m, ArH)	367	1720, 1672	260.9 (3.21), 213.9 (1.54)

[a] Elemental analyses: **4a** (Found: C, 69.3; H, 5.4; N, 14.7. $C_{17}H_{17}N_3O_2$ requires C, 69.15; H, 5.76; N, 14.23%); **4b** (Found: C, 62.4; H, 5.0; N, 12.43. $C_{17}H_{17}N_3O_4$ requires C, 62.38; H, 5.19; N, 12.84%); **4c** (Found: C, 61.9; H, 4.9; N, 12.6. $C_{17}H_{17}N_3O_4$ requires C, 62.38; H, 5.19; N, 12.84%); **4f** (Found: C, 62.5; H, 5.7; N, 21.2. $C_{17}H_{19}N_5O_2$ requires C, 62.75; H, 5.84; N, 21.53%); **4g** (Found: C, 70.6; H, 6.5; N, 12.6. $C_{19}H_{21}N_3O_2$ requires C, 70.58; H, 6.50; N, 13.00%); **4h** (Found: C, 69.9; H, 5.9; N, 12.5. $C_{19}H_{21}N_3O_2$ requires C, 70.58; H, 6.50; N, 13.00%); **4j** (Found: C, 63.8; H, 5.8; N, 11.5. $C_{19}H_{21}N_3O_4$ requires C, 64.22; H, 5.91; N, 11.83%); **4l** (Found: C, 64.2; H, 5.8; N, 11.5. $C_{19}H_{21}N_3O_4$ requires C, 64.22; H, 5.91; N, 11.83%); **4m** (Found: C, 55.5; H, 3.9; N, 11.6. $C_{17}H_{15}Cl_2N_3O_2$ requires C, 56.04; H, 4.12; N, 11.53%); [b] Solvent of crystallization: methanol–ether.

ation. However, 3-alkyl-6-methyl-1,3-oxazine-2,4(3*H*)-diones did not react with arylamines **3**.

Thus, less reactive arylamines react at C-2 of **1** at higher temperature than alkylamines, to form ketoureas **2**. Unlike alkyl N-1, the aryl N-1 of **2** is not reactive towards the carbonyl group. In the presence of excess of arylamine, enhancement of electrophilicity of carbonyl carbon through imine or acid induced iminium cation formation facilitates its interaction with aryl N-1 and formation of 1-aryluracil derivatives. Consequently heating of **1** with arylamines, (i) in refluxing acetic acid, (ii) on dry heating (150–160 °C) or subsequent refluxing in acetic acid provide synthetic methodologies for 1-aryl-6-methyluracils **5**.

Experimental

M.p.s were recorded in capillaries and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on JNM PMX 60 and Brucker AC 200 instruments for solutions in $CDCl_3$–[$^2H_6$]DMSO or TFA using Me_4Si as internal standard. IR and UV spectra were recorded on Pye-Unicam SP3-300 spectrophotometer and Shimadzu uv-240 instruments. Mass spectra (70 eV) were taken on a JEOL JMS-D 300 instrument at CDRI Lucknow.

Reactions of 6-*Methyl*-1,3-*oxazine*-2,4(3H)-*dione* **1** *with Arylamines* **3**.—(A) *Isopentanol. General procedure.* A solution of dione **1** (0.01 mol) and arylamine **3** (0.02 mol) in isopentanol was refluxed and the reaction was monitored by TLC. After completion (3–10 h), the solvent was removed under reduced pressure and the residue was crystallized from methanol–ether. The arylamines, **3a–d**, **f**, **h**, **i**, **k**, **l** gave their respective compound **5** (Table 1) and **3g**, **j**, **m** gave their respective compound **4**. Reaction of **1** and **3e** gave compound **9**. The termination of the reaction of **3a**, **c**, **f**, **h**, **i**, **k**, **l** after 2–5 h gave the respective compound **4** (Table 2).

(B) *Dry Heating. General procedure.* A mixture of dione **1** (0.01 mol) and arylamine (**3**, 0.02 mol) was heated in an oil bath at 150–160 °C. After completion of the reaction (3–8 h, TLC), the solid mass was triturated with methanol–ether. The aryl-

Table 3 Uracils **5**[a]

	Yield (%) (*t*/h)					
	i	ii	iii	iv	v	vi
5a	90 (3)	40 (6)	80 (4)	70 (2)	80 (2)	80 (2)
5b	*b*	90 (2.5)	31 (5)	55 (2)	62 (3)	53 (3)
5c	88 (5)	55 (9–10)	44 (4)	42 (3)	50 (3)	30 (3)
5d	90 (4)	48 (3)	40 (3)	*d*	*d*	*d*
5e	*c*	*e*	*c*	*d*	*d*	*d*
5f	*c*	40 (2–3)	90 (4)[f]	45 (3)	90 (2)[f]	30 (5)
5g	*b*	*b*	70 (5)	*g*	70 (3)	38 (8)
5h	*b*	50 (6–7)	35 (5)	60 (5)	94 (2)	48 (8)
5i	65 (6)	42 (7–8)	94 (3)	*d*	*d*	*d*
5j	*b*	*b*	55 (4)	*g*	65 (2)	12 (5)
5k	77 (8)	50 (7–8)	20 (3)	*d*	*d*	*d*
5l	*b*	47 (8–9)	65 (3)	50 (4)	72 (2)	48 (3)
5m	*b*	*b*	40 (4)	*g*	66 (3)	31 (3)

[a] Mixture of **1** and **3**: (i) heated at 150–160 °C; (ii) refluxed in isopentanol; (iii) refluxed in acetic acid. **4** Heated (iv) in isopentanol; (v) in acetic acid; (vi) in PPA. [b] Compound **4** is formed. [c] Unidentified product. [d] Compound **4** is not available. [e] Compound **9** is formed. [f] Compound **10** is formed. [g] Compound **4** remains unchanged.

amines **3a**, **c**, **d**, **i**, **k** gave corresponding compounds **5** (Table 1), but **3b**, **g**, **h**, **j**, **l**, **m** gave respective compounds **4** (Table 2).

(C) *Acetic acid. General procedure.* A solution of dione **1** (0.01 mol) and arylamine **3** (0.02 mol) in acetic acid was refluxed and the reaction was monitored by TLC. After the completion (3–5 h), acetic acid was removed under reduced pressure. The solid residue was crystallized from methanol–ether to isolate a white solid. Arylamines **3a–d**, **g–m** gave corresponding compounds **5** and **3f** gave compound **10** (Table 1).

Reactions of Compounds **4**.—(A) *Isopentanol.* The compounds **4** were refluxed in isopentanol for 2–10 h. After completion (TLC), isopentanol was removed under reduced pressure and the solid residue was crystallized from methanol–ether to give respective compounds **5** (Table 1).

(B) *Polyphosphoric acid* (PPA). The compounds **4** were heated in PPA at 120 °C for 2–8 h. After completion (TLC), water was added to the mixture and the compound was extracted with chloroform. The solvent was distilled off and the residue was crystallized to obtain respective compounds **5** (Table 1).

(C) *Acetic acid.* The compounds **4** were refluxed in acetic acid for 2–3 h. Acetic acid was removed under reduced pressure and the solid residue was crystallized from methanol–ether to give compounds **5**. Dione **1** with **3f** gave compound **10** (Table 1).

Acknowledgements

Thanks are due to CSIR for financial assistance and to the UGC for COSIST and SAP programmes.

References

1 H. Singh, P. Aggarwal and S. Kumar, *J. Chem. Soc., Perkin Trans. 1*, 1992, 1139.
2 D. J. Brown, in *Comprehensive Heterocyclic Chemistry—The Structure, Reactions, Synthesis and Uses of Heterocyclic Compounds*, vol. 3, ed. A. R. Katritzky and C. W. Rees, Pergamon, 1984, pp. 57–157.
3 T. S. Rao and C. B. Reese, *J. Chem. Soc., Chem. Commun.*, 1989, 997.
4 D. Bergstrom, P. Beal, A. Husain, R. Lind and J. Jenson, *J. Am. Chem. Soc.*, 1989, **111**, 374 and refs. therein.
5 I. Matsurra, T. Ueda, N. Murakmi, S. Nagai and J. Sakakibara, *J. Chem. Soc., Perkin Trans. 1*, 1991, 2821.
6 M. Hedayatullah, Roger, *C.R. Hebd. Seances Acad. Sci., Ser. B*, 1986, **303**, 195.
7 P. Singh, K. Deep and H. Singh, *J. Chem. Res.*, 1984, (*S*) 71; (*M*) 0636.
8 H. Singh, P. Aggarwal and S. Kumar, *Synthesis*, 1990, 520.
9 E. C. Muller, *Tetrahedron Lett.*, 1991, **32**, 6539.
10 S. Ahmed, R. Lofthouse and G. J. Shaw, *J. Chem. Soc., Perkin Trans. 1*, 1976, 1969.
11 T. Kinoshita, M. Takeuchi, M. Kondoh and S. Furukawa, *Chem. Pharm. Bull.*, 1989, **37**, 2026.
12 (*a*) R. N. Lacey, *J. Chem. Soc.*, 1954, 845; (*b*) T. Kinoshita, S. Odowara and K. Fukumara, *J. Heterocycl. Chem.*, 1985, **22**, 1573.
13 H. I. Skulnick and W. Wierenga, *Heterocycles*, 1985, **23**, 1685.
14 T. Kinoshita, H. Tanaka and S. Furukawa, *Chem. Pharm. Bull.*, 1986, **34**, 1809.
15 T. L. Davis and K. C. Blanchard, *Org. Synth.*, Coll. vol. 2, 1941, 453.
16 C. M. Desai, *J. Indian Chem. Soc.*, 1954, **31**, 50.
17 R. K. Ralph, G. Shaw and R. N. Naylor, *J. Chem. Soc.*, 1959, 1169.
18 H. Singh and S. Kumar, *J. Chem. Res.*, 1987, (*S*), 390; (*M*), 3201.

Paper 2/06520G
Received 8*th December* 1992
Accepted 14*th December* 1992