Heterocyclic transformations. Part 7. Unprecedented transformations of 1,3-dialkyl-5-formyluracils to 1,3-dialkyl-7-hydroxyquinazolines

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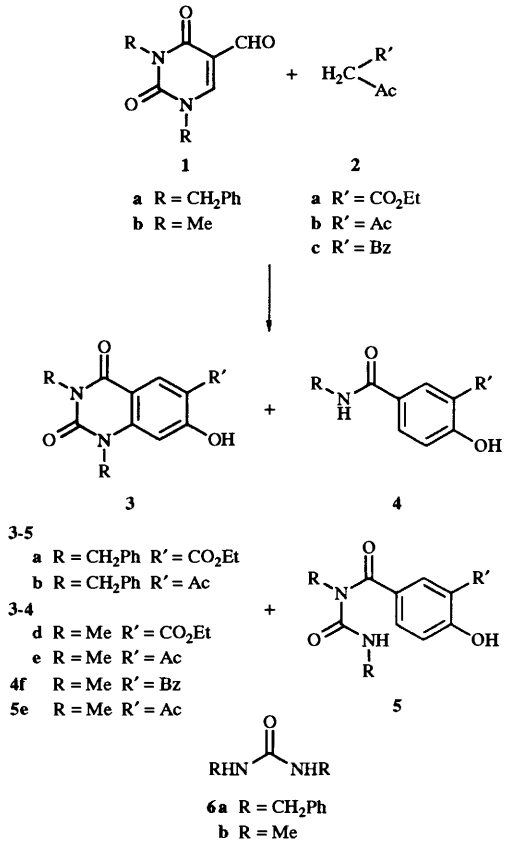
1,3-Dialkyl-5-formyluracil reacts with ethyl acetoacetate, acetylacetone, benzoylacetone, acetoacetamide and acetoacetanilide under phase transfer catalytic conditions to provide exclusively the annulation products: 6-substituted-1,3-dialkyl-7-hydroxyquinazolines or/and also 4-hydroxybenzamide derivatives. Similar reaction with cyanoacetamide provides 6-cyano-7-hydroxy-1,3-dimethylpyrido[2,3-*d*]pyrimidine. The reaction mechanism prevailing in these reactions has been rationalized.

Uracil, encompassing enaminone and urea moieties, by virtue of its unique reactivity pattern towards 1,2- or 1,3-binucleophiles followed by varied ring-opening modes and intramolecular cyclizations involving elimination of N^1-C^2 or N^1-C^2-N^3 units, constitutes a versatile synthon for a variety of ring-transformation products.[1] The ease of derivatization of uracils further facilitates the use of this approach for the design of tailor-made synthesis.[2] Since, earlier, we had beneficially used phase transfer catalytic (PTC) conditions for achieving synthetically useful chemoselective transformations of heterocycles,[3] we planned the investigations of the reactions of 1,3-dialkyl-5-formyluracils with α-substituted acetones and α-substituted amides under similar conditions. As a consequence, it has been discovered that these reactions provide annulation products– quinazoline **3** and pyridopyrimidine **17** derivatives exclusively and/or also benzene/pyridine derivatives. The formation of **3** and **17** presents an unprecedented case where all constituents of 5-formyluracil and carbanion precursors remain intact in the final product.

1,3-Dibenzyl-5-formyluracil **1a** reacted with ethyl acetoacetate under solid–liquid PTC conditions (DMF–K_2CO_3–$TBAHSO_4$)† at 20 ± 2 °C to give three products. The highest R_F component (15%, mp 150 °C, M^+ *m/z* 430) in its ^{1}H NMR spectrum shows two downfield 1 H singlets at δ 6.59 and 8.78 along with dibenzyl and ester signals which indicate the presence of tetrasubstituted aryl ring with unsubstituted *para* positions. In its mass spectrum, the parent ion peak at 430 (M^+) points to the product being a dehydro condensate of **1a** and ethyl acetoacetate and its ^{13}C and ^{1}H NMR data are consistent with structure **3a**. The second component (25%, mp 140 °C, M^+ *m/z* 298) in its ^{1}H NMR spectrum shows three 1 H signals at δ 6.98 (d, *J* 8.7 Hz), 7.65 (dd, *J* 8.7, 2.3 Hz) and 8.33 (d, *J* 2.3 Hz) along with benzyl and ethyl signals, which indicate the presence of trisubstituted aryl ring with unsubstituted *ortho*- and *meta*-positions. From these spectral data, its ^{13}C NMR and elemental analysis, it could be assigned the structure **4a**. The third component [8%, mp 166–167 °C (lit.,[4] mp 168 °C), M^+ *m/z* 240] was found to be 1,3-dibenzylurea‡

For optimizing the yield of quinazoline derivative **3a**, the reaction of **1a** and ethyl acetoacetate was performed at different temperatures. On performing the reaction at 0–10 °C, an additional product (8%, mp 81 °C, M^+ *m/z* 432) was isolated. In its ^{1}H NMR spectrum the presence of one benzyl CH_2 unit as doublet and the other one as a singlet along with ethyl and three 1 H signals in the aromatic region as in compound **4a**, was assigned structure **5a**, which is in consonance with its ^{13}C NMR and elemental analysis. At a reaction temperature below 0 °C, this reaction did not occur whilst at 35–40 °C, the yield of **3a** decreased to 8% only. Since compound **3a** seems to be formed as a result of the oxidation of the initial annulation product, the reactions of **1a** with ethyl acetoacetate were performed in the presence of oxidizing agents like $FeCl_3$ or benzoquinone or MnO_2 or air. However, in each case, the yield of **3a** remained nearly the same. Therefore, a stirred reaction mixture under PTC conditions at 20 ± 2 °C constitutes optimum conditions for the preparation of the quinazoline derivative **3a**. Hence all other reactions were performed under these conditions.



Scheme 1

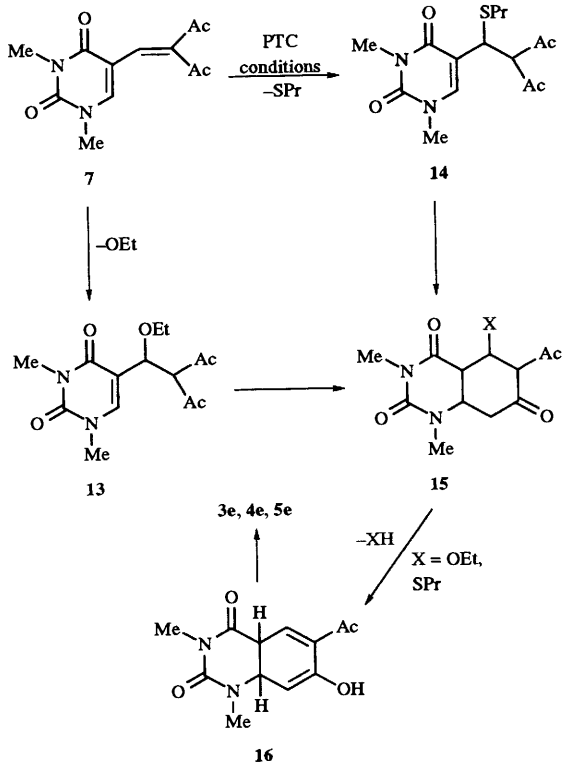
† DMF = dimethylformamide, $TBAHSO_4$ = tetrabutylammonium hydrogen sulfate.

‡ Earlier, Hirota *et al.*[1f] reported that 1,3-dimethyl-5-formyluracil and ethyl acetoacetate react in refluxing ethanol containing potassium hydroxide to form ethyl 3-(ethoxycarbonyl)-4-hydroxybenzoate (37%) and 3-(ethoxycarbonyl)-4-hydroxy-*N*-methylbenzamide.

The reactions of **1a** with (i) acetylacetone **2b** and (ii) benzoylacetone **2c** gave (i) **3b** (6%), **4b** (25%), **5b** (8%) and **6a** (10%) and (ii) **3c** (2%), **4c** (35%), **5c** (25%) and **6a** (10%), respectively. However, phenylacetone and acetone with **1a** gave a multitude of products which could not be isolated.

Further, in order to determine the effect of *N*-substituents in **1**, on the product distribution, the reactions of 1,3-dimethyl-5-formyluracil **1b** were performed with α-substituted acetone derivatives. 1,3-Dimethyl-5-formyluracil **1b** with ethyl acetoacetate gave **3d** (28%), **4d** (25%) and 1,3-dimethylurea[5] (10%) while the reaction of **1b** with (i) acetylacetone and (ii) benzoylacetone gave (i) **5e** (36%), **3e** (14%), **4e** (8%) and **6b** (4%) and (ii) **4f** (70%) and **6b** (6%). Compound **1b** with phenylacetone and acetone gave a multitude of products whilst **1b** failed to react with diethyl malonate and malonamide. From the nature and ratio of the products formed in the above reactions of **1b**, any discernible role of N-substituent on the mode of the reaction is not observed.

The formation of compounds **3–5** in these reactions could conveniently be visualized to proceed through the formation of analogues of the intermediate **7** as proposed by Hirota[1f] for the formation of benzoate and benzamide derivatives from **1b** and **2b** in the presence of NaOEt–EtOH. But **7** prepared from **1b** and **2b** remained unchanged under PTC conditions of the reaction even after 24 h. This observation ruled out the participation of the intermediates **9** and **11** in these reactions. Since CPK models of **7** and **8** (R′ = Ac) point to relative ease of approach of terminal methyl carbon (Ac) towards uracil C-6 in **8** over that in **7**, we argued in favour of the intermediacy of **8** in these reactions. Further, we found that even PTC (DMF–K_2CO_3–$TBAHSO_4$) reaction of **7** performed in the presence of propane-1-thiol gave products **3e** (8%), **4e** (20%), **5e** (17%) and 1,3-dimethylurea (6%) (Scheme 2). Evidently, the intermediacy of **14** has been evoked. Even in the reaction of **7** with OEt, again **13** (an analogue of **8**) could be formed first. The intermediates **13** and **14** could cyclize to **15** which *via* **16** could provide **3e**, **4e** and **5e**. Hence, in general, it might be concluded that the



Scheme 2

reactions of **1** with α-substituted acetones proceed through sequential intermediacy of **8**, **10** and **12** (Scheme 3) and the last mentioned undergoing eliminations through paths a, b and c to form **3**, **4** and **5**, respectively. The observations that **5a** is isolated in the case of the reaction of **1a** and ethyl acetoacetate and that on further stirring under PTC conditions in the presence of aniline it provides **4a** and 1-benzyl-3-phenylurea, point towards the formation of **4** both through path a and elimination of isocyanate from **5**.

Therefore, α-substituted acetones effectively behave as precursors for the 1,3-bis-carbanions and react at electrophilic CHO and C-6 of uracils to give ring transformed products.

For determining the scope of the annulation, the reaction of **1b** with a substituted acetamide, cyanoacetamide, was performed under PTC conditions. It gave only **17** (52%, mp 263–265 °C, M^+ *m/z* 234). Hence, the nitrogen nucleophile has also reacted at C-6 of uracil in the reaction sequence to form the ring annulation product.

In order to evaluate the competition between amide nitrogen and acetyl carbon in forming the bond at C-6 of uracil in the intermediate **18**, we performed the reactions of **1b** with acetoacetanilide **19** (R = Ph) and acetoacetamide **19** (R = H) under PTC conditions. The reaction of **1b** with **19** (R = Ph and H) gave, respectively, the quinazoline derivatives **3g** (55%) and **3h** (62%); formation of the corresponding pyridopyrimidine derivatives from the intermediate **18** or the elimination reaction products accompanying the final cyclization step were not noticed.

Therefore, in the reactions of **1b** with acetoacetamide and acetoacetanilide, the reaction of the anion of $COCH_3$, **18**, at uracil C-6 in the intermediate is favoured over that of the nitrogen of the amide unit.

Thus, 5-formyluracil derivatives with α-substituted acetones and acetamides under mild PTC conditions at relatively low temperature provide oxidative annulation products: quinazoline and pyridopyrimidine derivatives either exclusively or along with elimination transformation products; this contrasts with earlier reports where, under basic conditions, formation of only elimination transformation products were reported.

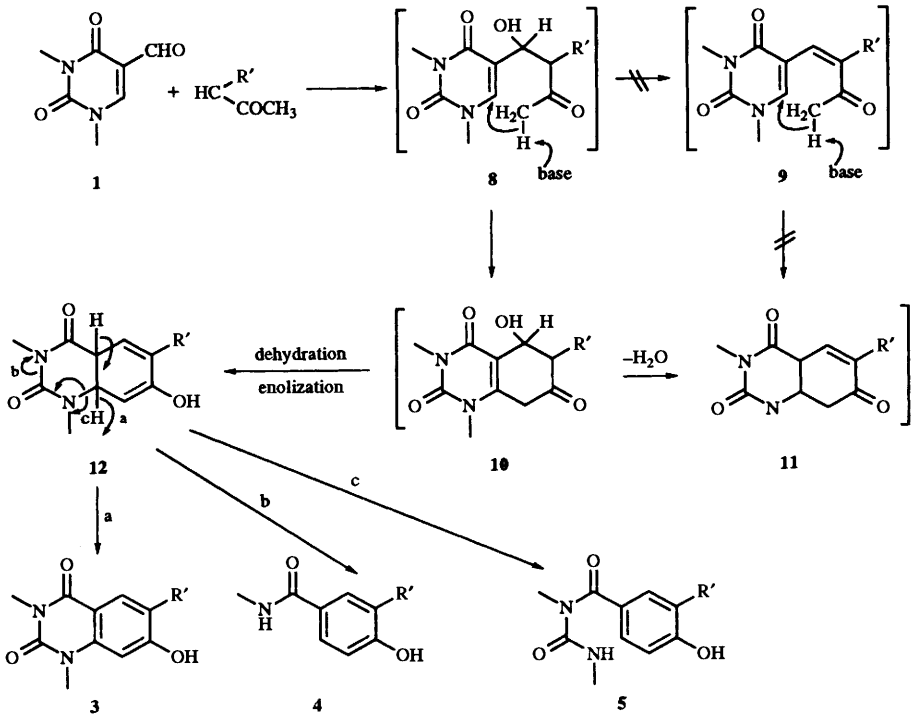
Experimental

Mps were determined in capillaries and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on JEOL JNM PMX 60 MHz and Bruker AC 200 MHz instruments using Me_4Si as internal standard. *J* Values are given in Hz. IR and UV spectra were recorded on Pye-Unicam SP3-300 spectrophotometer and Shimadzu UV-240 instruments, respectively. Mass spectra were recorded on VG micromass 7070 F and GCMS-QP2000A mass spectrometers. Thin layer chromatography was performed on pre-coated TLC plates (silica gel G or silica gel 60 HF_{254}). Column chromatography was carried out using silica gel (60–120).

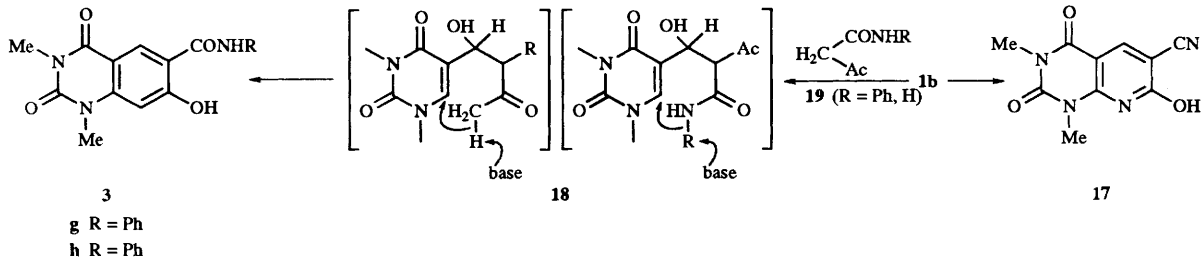
1,3-Dibenzyluracil

Uracil (11.2 g, 0.1 mol) and benzyl chloride (25.6 g, 0.2 mol) were stirred at 50 °C under PTC conditions using K_2CO_3 as base, MeCN as solvent and triethylbenzylammonium-chloride (TEBA) as catalyst, for 12 h. The suspension was filtered and the filtrate was evaporated under reduced pressure to give a solid which upon crystallization from ethanol gave pure 1,3-dibenzyluracil (26 g, 80%), mp 74–75 °C (lit.,[5] mp 75–76.5 °C).

Earlier,[5] this compound had been prepared (80%) by heating uracil and benzyl bromide in refluxing acetone in the presence of K_2CO_3 for 50 h. The present method, therefore, has the advantage of using cheaper benzyl chloride and a shorter reaction time.



Scheme 3



Scheme 4

1,3-Dibenzyl-5-formyluracil 1a

A mixture of 1,3-dibenzyluracil (7 g) and Vilsmeier–Haack reagent prepared from $POCl_3$ (7 cm^3) and ice-cooled dry DMF (40 cm^3) were heated under reflux for 45 min. The solvent was distilled off under reduced pressure and the residue was poured onto ice (200 g) and extracted with $CHCl_3$. The solvent was distilled off and the residue was crystallized from ethanol to give **1a** (65%), mp 105 °C; *m/z* 320 (M^+); $\delta_H(CDCl_3)$ 5.03 (2 H, s, CH_2), 5.17 (2 H, s, CH_2), 7.02–7.25 (10 H, m, ArH), 8.05 (1 H, s, C_6H) and 10.02 (1 H, s, CHO) (Found: C, 71.3; H, 4.9; N, 8.55. $C_{19}H_{16}N_2O_3$ requires C, 71.25; H, 5.00; N, 8.75%).

Reactions of 1,3-dialkyl-5-formyluracils 1 with nucleophiles

General procedure. A solution of the 1,3-dialkyl-5-formyluracil **1** (3 mol) and active methylene compound **2** (3.6 mmol) in DMF (20 cm^3) containing potassium carbonate (1.69 g, 1.2 mmol) (base) and $TBAHSO_4$ (15–20 mg) (catalyst) was stirred at 20 ± 2 °C (or the alternative temperature where recorded). The reaction was monitored by TLC and after completion (8–12 h) the suspended solid was filtered off and washed with ethyl acetate. Solvent was distilled from the combined filtrate and washings under reduced pressure and the residue was column chromatographed on silica gel with hexane and hexane–ethyl acetate (9:1) as eluents. Results for the compounds thus obtained are given below.

Reaction of 1a with ethyl acetoacetate. 1,3-*Dibenzyl*-6-*ethoxycarbonyl*-7-*hydroxyquinazoline*-2,4(1H,3H)-*dione* **3a** (15%).—Mp 150 °C (ethanol); *m/z* 430 (M^+); $\delta_H(CDCl_3)$ 1.41 (3 H, t, 7, CH_3), 4.41 (2 H, q, 7, OCH_2), 5.30 (4 H, s, NCH_2), 6.59 (1 H, s, 8-H), 7.32–7.52 (10 H, m, ArH), 8.78 (1 H, s, 5-H) and 11.43 (1 H, br, OH, exchanges with D_2O); $\delta_C(CDCl_3)$ 14.15 (q, CH_3), 45.16 (t, CH_2), 47.77 (t, CH_2), 62.02 (t, CH_2), 101.73 (d, CH), 126.51 (d, ArH), 127.73 (d, ArH), 127.89 (d, ArH), 128.50 (d, ArH), 129.05 (d, ArH), 133.38 (d, CH) (overlapping doublets), 135.01 (s), 136.86 (s), 145.10 (s), 151.47 (s), 160.86 (s), 166.06 (s), 166.26 (s), 169.18 (s) and 169.29 (s); ν_{max}(KBr)/cm^{-1} 1670 (C=O) and 1620 (C=O); λ_{max}(EtOH)/nm 305.8 (0.60×10^4), 278.8 (0.183×10^4) and 248.4 (1.7×10^4) (Found: C, 68.8; H, 5.4; N, 6.1. $C_{25}H_{22}N_2O_5$ requires C, 69.01; H, 4.89; N, 6.40%).

N-Benzyl-3-*ethoxycarbonyl*-4-*hydroxybenzamide* **4a** (25%).—Mp 140 °C (EtOH); *m/z* 299 (M^+); $\delta_H(CDCl_3)$ 1.40 (3 H, t, 7, OCH_2CH_3), 4.43 (2 H, q, 7, OCH_2CH_3), 4.61 (2 H, d, 5.7, NH–CH_2, on D_2O exchange collapses to singlet), 6.98 (1 H, d, 8.7, C-5 H), 7.26–7.35 (5 H, m, ArH), 7.65–7.91 (1 H, dd, 8.7 and 2.13, 6-H), 8.33 (1 H, d, 2.3, 2-H) and 11.17 (1 H, br, OH, exchanges with D_2O); δ_C 14.20 (q, CH_3), 44.01 (t, CH_2), 61.93 (t, CH_2), 112.41 (s), 117.76 (d, CH), 125.37 (s), 127.61 (d, CH), 127.90 (d, CH), 128.76 (d, CH), 129.52 (d, CH), 132.95 (d, CH), 138.23 (s), 163.90 (s), 166.09 (s) and 169.60 (s); ν_{max}(KBr)/cm^{-1} 1675 (C=O), 1640 (C=O) and 1595 (C=O); λ_{max}(EtOH)/nm 305.8

(0.38 × 10^4) and 246.0 (1.31 × 10^4) (Found: C, 67.7; H, 4.95; N, 4.2. $C_{17}H_{17}NO_4$ requires C, 68.12; H, 5.54; N, 4.40%).

1,3-*Dibenzylurea* **6a**.—(10%); mp 166–167 °C (lit.,[4] mp 168 °C); *m/z* 240 (M^+).

Reaction of 1a with ethyl acetoacetate under PTC conditions at 0–10 °C. *Compounds* **3a** (10%), **4a** (25%) *and* **6a** (8%). 1,3-*Dibenzyl*-1-(3-*ethoxycarbonyl*-4-*hydroxybenzoyl*)*urea* **5a** (8%).—Mp 81 °C (ethanol); *m/z* 299 (M^+ − Ph − CH_2 − NH − CO); $\delta_H(CDCl_3)$ 1.33 (3 H, t, 7, CH_3), 1.41 (1 H, br, exchanges with D_2O), 4.33 (2 H, q, 7, OCH_2), 4.56 (2 H, d, 5.6, $NHCH_2$, on D_2O exchange collapses to singlet), 5.02 (2 H, s, NCH_2), 6.94 (1 H, d, 8.6, 5-H), 7.07–7.47 (10 H, m, ArH), 7.53 (1 H, dd, 8.6 and 2.16, 6-H), 7.86 (1 H, d, 2.16, 2-H) and 11.13 (1 H, br, OH, exchanges with D_2O); δ_C 14.10 (q, CH_3), 44.88 (t, CH_2), 50.46 (t, CH_2), 61.93 (t, CH_2), 101.69 (d, CH), 112.21 (s), 117.89 (d, CH), 126.56 (d, ArH), 127.29 (d, ArH), 127.85 (d, ArH), 128.67 (d, ArH), 129.06 (d, ArH), 129.28 (d, ArH), 134.07 (d, CH), 137.87 (s), 138.07 (s), 155.12 (s), 163.47 (s), 169.18 (s), 169.29 (s) and 173.94 (s); ν_{max}(KBr)/cm^{-1} 3410 (NH) and 1660 (C=O); λ_{max}(EtOH)/nm 307.6 (0.164 × 10^4) and 242.0 (0.945 × 10^4) (Found: C, 66.7; H, 4.7; N, 5.0. $C_{25}H_{24}N_2O_5$ requires C, 67.07; H, 5.25; N, 5.40%).

Reaction of 1a with acetylacetone. 1,3-*Dibenzyl*-6-*acetyl*-7-*hydroxyquinazoline*-2,4(1H,3H)-*dione* **3b** (6%).—Mp 139 °C (EtOH); *m/z* 400 (M^+); $\delta_H(CDCl_3)$ 2.67 (3 H, s, CH_3), 5.31 (4 H, s, 2 × CH_2), 6.58 (1 H, s, 8-H), 7.25–7.34 (10 H, m, ArH), 8.67 (1 H, s, 5-H) and 12.79 (1 H, br, exchanges with D_2O); $\delta_C(CDCl_3)$ 26.11 (q, CH_3), 45.01 (t, CH_2), 51.32 (t, CH_2), 101.51 (d, CH), 127.49 (d, CH), 127.98 (d, CH), 128.01 (d, CH), 128.61 (d, CH), 129.86 (d, CH), 129.99 (d, CH), 133.72 (d, CH), 136.84 (s), 137.01 (s), 146.82 (s), 151.51 (s), 161.32 (s), 166.53 (s), 166.93 (s), 170.03 (s) and 170.22 (s); ν_{max}(KBr)/cm^{-1} 1640 (C=O); λ_{max}(EtOH)/nm 307.2 (0.54 × 10^4) and 254.3 (1.98 × 10^4) (Found: C, 68.1; H, 2.9; N, 5.8. $C_{24}H_{20}N_2O_4$ requires C, 67.78; H, 3.25; N, 6.15%).

3-*Acetyl*-N-*benzyl*-4-*hydroxybenzamide* **4b** (8%).—Mp 161 °C (EtOH); *m/z* 245 (M^+); $\delta_H(CDCl_3)$ 2.55 (3 H, s, CH_3), 4.55 (2 H, d, $NHCH_2$, on D_2O exchange collapses to singlet), 6.79 (1 H, d, 8.7, 5-H), 7.07–7.35 (5 H, m, ArH), 7.79–7.85 (1 H, dd, 8.6 and 2.16, 6-H) and 8.31 (1 H, d, 2.16, 2-H); $\delta_C(CDCl_3)$ 24.15 (q, CH_3), 44.88 (t, CH_2), 101.85 (d, CH), 113.01 (s), 117.03 (d, CH), 126.37 (d, ArH), 128.07 (d, ArH), 128.71 (d, ArH), 133.01 (d, CH), 139.44 (s), 140.01 (s), 157.71 (s), 170.31 (s) and 175.11 (s); ν_{max}(KBr)/cm^{-1} 3280 (NH) and 1625 (C=O); λ_{max}(EtOH)/nm 304 (0.43 × 10^4) and 251.0 (1.4 × 10^4) (Found: C, 70.8; H, 5.1; N, 5.5. $C_{16}H_{15}NO_3$ requires C, 71.01; H, 5.10; N, 5.20%).

1-(3-*Acetyl*-4-*hydroxybenzoyl*)-1,3-*dibenzylurea* **5b** (27%).—Mp 102 °C (EtOH); *m/z* 402 (M^+); $\delta_H(CDCl_3)$ 1.59 (1 H, br, NH), 2.18 (3 H, s, CH_3), 4.57 (2 H, d, $NHCH_2$, on D_2O exchange collapses to singlet), 5.00 (2 H, s, NCH_2), 6.86 (1 H, d, 8.6, 5-H), 7.07–7.33 (10 H, m, ArH), 7.55–7.58 (1 H, dd, 8.6 and 2.16, 6-H), 8.56 (1 H, d, 2.16, 2-H) and 12.45 (1 H, br, exchanges with D_2O); $\delta_C(CDCl_3)$ 14.10 (q, CH_3), 44.86 (t, CH_2), 50.52 (t, CH_2), 101.69 (d, CH), 112.06 (s), 116.89 (d, CH), 126.35 (d, ArH), 127.41 (d, ArH), 127.71 (d, ArH), 128.87 (d, ArH), 129.74 (d, ArH), 134.81 (d, CH) (collapsing doublets), 138.01 (s), 139.34 (s), 156.78 (s), 162.01 (s), 169.01 (s), 170.31 (s) and 174.11 (s); ν_{max}(KBr)/cm^{-1} 3300 (NH) and 1640 (C=O); λ_{max}(EtOH)/nm 326 (0.15 × 10^4) and 240.8 (1.02 × 10^4) (Found: C, 71.7; H, 4.8; N, 6.6. $C_{24}H_{22}N_2O_4$ requires C, 72.00; H, 5.00; N, 7.00%).

1,3-*Dibenzylurea*[4] (10%).

Reaction of 1a with benzoyl acetone. 6-*Benzoyl*-1,3-*dibenzyl*-7-*hydroxyquinazoline*-2,4(1H,3H)-*dione* **3c** (2%).—Mp 173 °C (EtOH); *m/z* 462 (M^+); $\delta_H(CDCl_3)$ 4.57 (4 H, s, 2 × CH_2), 6.72 (1 H, s, 8-H), 7.32–7.68 (15 H, m, ArH), 8.78 (1 H, s, 5-H) and 12.59 (1 H, br, exchanges with D_2O); $\delta_C(CDCl_3)$ 45.58 (t, CH_2), 48.98 (t, CH_2), 107.02 (d, CH), 125.5 (d, CH), 125.99 (d, CH), 126.03 (d, CH), 126.50 (d, CH), 126.88 (d, CH), 127.45 (d, CH), 127.98 (d, CH), 128.33 (d, CH), 129.04 (d, CH), 133.89 (d, CH), 137.54 (s), 139.56 (s), 146.78 (s), 149.73 (s), 150.47 (s), 160.78 (s), 167.34 (s), 165.24 (s), 168.77 (s) and 202.44 (s); ν_{max}(KBr)/cm^{-1} 1650 (C=O) and 1625 (C=O); λ_{max}(EtOH)/nm 310.0 (0.67 × 10^4), 279 (0.24 × 10^4) and 246.2 (1.87 × 10^4) (Found: C, 75.0; H, 4.5; N, 5.8. $C_{29}H_{22}N_2O_4$ requires C, 75.32; H, 4.76; N, 6.06%).

3-*Benzoyl*-N-*benzyl*-4-*hydroxybenzamide* **4c** (34%).—Mp 160–162 °C (EtOH); *m/z* 331 (M^+); $\delta_H(CDCl_3)$ 4.57 (2 H, d, 5.6, $NHCH_2$, on D_2O exchange collapses to singlet), 6.72 (1 H, d, 8.6, 5-H), 7.30–7.70 (5 H, m, ArH), 7.63–7.88 (1 H, dd, 8.7 and 2.15, 6-H), 8.19 (1 H, d, 2.15, 2-H), 12.29 (1 H, b, exchanges with D_2O); $\delta_C(CDCl_3)$ 44.00 (t, CH_2), 112.02 (s), 118.34 (d, CH), 124.61 (s), 126.04 (d, CH), 126.62 (d, CH), 127.88 (d, CH), 128.11 (d, CH), 128.51 (d, CH), 128.78 (d, CH), 130.71 (d, CH), 135.15 (d, CH), 137.23 (s), 157.69 (s), 165.33 (s), 165.62 (s) and 201.23 (s); ν_{max}(KBr)/cm^{-1} 3410 (NH) and 1620 (C=O); λ_{max}(EtOH)/nm 304.0 (0.45 × 10^4) and 249.2 (1.2 × 10^4) (Found: C, 74.2; H, 4.2; N, 3.9. $C_{21}H_{17}NO_3$ requires C, 74.54; H, 4.89; N, 4.22%).

1,3-*Dibenzyl*-1-(3-*benzoyl*-4-*hydroxybenzoyl*) *urea* **5c** (27%).—Mp 143 °C (EtOH); *m/z* 464 (M^+); $\delta_H(CDCl_3)$ 1.60 (1 H, br, exchanges with D_2O), 4.52 (2 H, d, 5.6, $NHCH_2$, on D_2O exchange collapses to singlet), 4.99 (2 H, s, CH_2), 7.15 (1 H, d, 8.7, 5-H), 7.19 (1 H, dd, 8.7 and 2.16, 6-H), 7.25–7.44 (15 H, m, ArH), 7.52 (1 H, d, 2.16, 2-H) and 12.24 (1 H, b, exchanges with D_2O); $\delta_C(CDCl_3)$ 45.03 (t, CH_2), 48.97 (t, CH_2), 103.35 (d, CH), 113.04 (s), 118.45 (d, CH), 126.78 (d, CH), 126.99 (d, CH), 127.45 (d, CH), 127.68 (d, CH), 128.03 (d, CH), 128.97 (d, CH), 129.05 (d, CH), 129.47 (d, CH), 129.89 (d, CH), 135.99 (d, CH), 139.78 (s), 139.98 (s), 155.59 (s), 155.87 (s), 163.47 (s), 169.78 (s), 173.33 (s) and 200.03 (s); ν_{max}(KBr)/cm^{-1} 3430 (NH) and 1640 (C=O); λ_{max}(EtOH)/nm 309.0 (0.23 × 10^4), 295.4 (0.12 × 10^4) and 243 (0.98 × 10^4) (Found: C, 74.9; H, 4.9; N, 5.8. $C_{29}H_{24}N_2O_4$ requires C, 75.32; H, 5.15; N, 6.04%).

1,3-*Dibenzylurea*[4] (8%).

Reaction of 1b with ethyl acetoacetate. 6-*Ethoxycarbonyl*-7-*hydroxy*-1,3-*dimethylquinazoline*-2,4(1H,3H)-*dione* **3d** (34%).—Mp 164 °C (EtOH); *m/z* 278 (M^+); $\delta_H(CDCl_3)$ 1.45 (3 H, t, 7, CH_3), 3.46 (3 H, s, NCH_3), 3.57 (3 H, s, NCH_3), 4.45 (2 H, q, 7, CH_2), 6.66 (1 H, s, 8-H), 8.73 (1 H, s, 5-H) and 11.53 (1 H, br, exchanges with D_2O); $\delta_C(CDCl_3)$ 14.18 (q, CH_3), 28.44 (q, CH_3), 31.08 (q, CH_3), 62.08 (t, CH_2), 100.82 (d, CH), 108.04 (s), 108.90 (s), 132.98 (d, CH), 145.54 (s), 151.21 (s), 160.99 (s), 166.28 (s) and 169.39 (s); ν_{max}(KBr)/cm^{-1} 1660 (C=O) and 1620 (C=O); λ_{max}(EtOH)/nm 317.8 (0.79 × 10^4), 277.4 (1.3 × 10^4) and 246.2 (1.92 × 10^4) (Found: C, 54.7; H, 5.5; N, 9.9. $C_{13}H_{14}N_2O_5$ requires C, 55.11; H, 5.03; N, 10.05%).

3-*Ethoxycarbonyl*-4-*hydroxy*-N-*methylbenzamide* **4d** (20%).—Mp 197 °C (EtOH); *m/z* 233 (M^+); $\delta_H(CDCl_3)$ 1.42 (3 H, t, 7, CH_3), 3.00 (3 H, d, 4.82, $NHCH_3$, on D_2O exchange collapses to singlet), 4.43 (2 H, q, 7, CH_2), 6.99 (1 H, d, 8.6, 5-H), 7.84–7.89 (1 H, dd, 8.7 and 2.3, 6-H), 8.30 (1 H, d, 2.3, 2-H) and 11.14 (1 H, br, exchanges with D_2O); $\delta_C(CDCl_3)$ 14.18 (q, CH_3), 26.72 (q, CH_3), 61.95 (t, CH_2), 112.35 (s), 117.26 (d, CH), 125.57 (s), 129.12 (d, CH), 133.80 (d, CH), 163.91 (s), 166.66 (s) and 169.70 (s); ν_{max}(KBr)/cm^{-1} 1670 (C=O) and 1595 (C=O); λ_{max}(EtOH)/nm 307.4 (0.39 × 10^4) and 245.2 (1.26 × 10^4) (Found: C, 58.8; H, 5.85; N, 6.3. $C_{11}H_{13}NO_4$ requires C, 59.19; H, 5.83; N, 6.28%).

1,3-*Dimethylurea* **6b** (9%); mp 140–141 °C (lit.,[5] mp 142 °C).

Reaction of 1b with acetylacetone. 6-*Acetyl*-7-*hydroxy*-1,3-*dimethylquinazoline*-2,4(1H,3H)-*dione* **3e** (14%).—Mp 126 °C; *m/z* 248 (M^+); $\delta_H(CDCl_3)$ 2.69 (3 H, s, $COCH_3$), 3.46 (3 H, s, NCH_3), 3.58 (3 H, s, NCH_3), 6.64 (1 H, s, 8-H), 8.64 (1 H, s, 5-H) and 11.01 (1 H, br, exchanges with D_2O); $\delta_C(CDCl_3)$ 25.01

(q, CH_3), 28.27 (q, CH_3), 31.51 (q, CH_3), 101.09 (d, CH), 109.38 (s), 109.99 (s), 133.57 (d, CH), 145.98 (s), 152.31 (s), 162.02 (s), 166.57 (s) and 195.90 (s); ν_{max}(KBr)/cm^{-1} 1660 (C=O) and 1640 (C=O); λ_{max}(EtOH)/nm 318.9 (0.69 × 10^4), 279 (1.2 × 10^4) and 248.8 (1.4 × 10^4) (Found: C, 57.75; H, 4.5; N, 11.0. $C_{12}H_{12}N_2O_4$ requires C, 58.06; H, 4.83; N, 11.29%).

3-*Acetyl*-4-*hydroxy*-N-*methylbenzamide* **4e** (15%).—170 °C (EtOH); *m/z* 193 (M^+); δ_H($CDCl_3$) 2.67 (3 H, s, $COCH_3$), 3.00 (3 H, d, $NHCH_3$, on D_2O exchange collapses to singlet), 6.97 (1 H, d, 8.7, 5-H), 7.77–7.82 (1H, dd, 8.7 and 2.1, 6-H), 8.31 (1 H, d, 2.1, 2-H) and 11.01 (1 H, br, exchanges with D_2O); δ_C($CDCl_3$) 26.74 (q, CH_3), 26.89 (q, CH_3), 118.33 (d, CH), 119.30 (s), 125.27 (s), 130.95 (d, CH), 133.79 (d, CH), 164.35 (s), 166.92 (s) and 204.57 (s); ν_{max}(KBr)/cm^{-1} 1650 (C=O) and 1625 (C=O); λ_{max}(EtOH)/nm 323.4 (0.49 × 10^4), 251.0 (1.67 × 10^4) and 245.4 (1.70 × 10^4) (Found: C, 61.9; H, 5.6; N, 7.5. $C_{10}H_{11}NO_3$ requires C, 62.18; H, 5.69; N, 7.25%).

1-(3-*Acetyl*-4-*hydroxybenzoyl*)-1,3-*dimethylurea* **5e** (36%).—Mp 115 °C (EtOH); *m/z* 250 (M^+); δ_H($CDCl_3$) 2.67 (3 H, s, $COCH_3$), 2.94 (3 H, d, $NHCH_3$, on D_2O exchange collapses to singlet), 3.27 (3 H, s, NCH_3), 7.04 (1 H, d, 8.7, 5-H), 7.58–7.83 (1 H, dd, 4.9 and 2.2, 6-H), 7.95 (1 H, d, 2.1, 2-H) and 13.00 (1 H, br, exchanges with D_2O); δ_C($CDCl_3$) 26.21 (q, CH_3), 26.91 (q, CH_3), 36.12 (q, CH_3), 112.06 (s), 117.00 (s), 118.17 (d, CH), 126.51 (s), 130.81 (d, CH), 134.71 (d, CH), 155.98 (s), 173.16 (s) and 190.02 (s); ν_{max}(KBr)/cm^{-1} 3310 (NH), 1670 (C=O) and 1640 (C=O); λ_{max}(EtOH)/nm 322.6 (0.59 × 10^4) and 246.4 (1.93 × 10^4) (Found: C, 57.9; H, 5.6; N, 11.1. $C_{12}H_{14}N_2O_4$ requires C, 57.60; H, 5.60; N, 11.04%).

1,3-*Dimethylurea*[5] (4%).

Reaction of 1b with benzoylacetone. 3-*Benzoyl*-4-*hydroxy*-N-*methylbenzamide* **4f** (70%).—Mp 144 °C (EtOH); *m/z* 255 (M^+); δ_H($CDCl_3$) 2.94 (3 H, d, $NHCH_3$, on D_2O exchange collapses to singlet), 7.08 (1 H, d, 8.7, 5-H), 7.49–7.70 (5 H, m, ArH), 7.84–7.89 (1 H, dd, 8.7 and 2.1, 6-H), 8.11 (1 H, d, 2.1, 2-H) and 12.26 (1 H, br, exchanges with D_2O); δ_C($CDCl_3$) 26.81 (q, CH_3), 118.54 (d, CH), 118.88 (s), 125.19 (s), 126.61 (d, CH), 129.21 (d, CH), 132.43 (d, CH), 133.04 (d, CH), 134.06 (d, CH), 137.52 (s), 165.46 (s), 166.96 (s) and 201.55 (s); ν_{max}(KBr)/cm^{-1} 1680 (C=O) and 1650 (C=O); λ_{max}(EtOH)/nm 331.2 (0.42 × 10^4), 257.0 (1.85 × 10^4) and 248.2 (1.93 × 10^4) (Found: C, 69.4; H, 5.0; N, 5.9. $C_{15}H_{13}NO_3$ requires C, 70.05; H, 5.09; N, 5.46%).

1,3-*Dimethylurea*[5] (6%).

Reaction of 1b with cyanoacetamide. 6-*Cyano*-7-*hydroxy*-1,3-*dimethylpyrido*[2,3-*d*]*pyrimidine*-2,4-*dione* **17** (58%).—Mp 238 °C (EtOH); *m/z* 232; δ_H($CDCl_3$ + TFA) 3.54 (3 H, s, NCH_3), 3.79 (3 H, s, NCH_3) and 8.78 (1 H, s, 5-H); δ_C($CDCl_3$ + DMSO) 28.30 (q, CH_3), 29.76 (q, CH_3), 91.46 (s), 102.55 (s), 114.95 (s), 142.83 (s), 145.07 (d, CH), 148.99 (s), 159.39 (s) and 166.70 (s); ν_{max}(KBr)/cm^{-1} 2210 (C≡N), 1730 (C=O) and 1650 (C=O) (Found: C, 43.0, H, 2.5; N, 19.2. $C_{10}H_8N_4O_3$ requires C, 43.40; H, 2.98; N, 19.53%).

Reaction of 1b with acetoacetanilide. 7-*Hydroxy*-1,3-*dimethyl*-6-(N-*phenylcarbamoyl*)*quinazoline*-2,4-*dione* **3g** (55%).—Mp 235–236 °C (EtOH); *m/z* 325 (M^+); δ_H($CDCl_3$ + [$^2H_6$]-DMSO) 2.96 (3 H, s, NCH_3), 3.17 (3 H, s, NCH_3), 6.89 (1 H, s, 8-H), 7.24–7.35 (5 H, m, ArH) and 8.25 (1 H, s, 5-H); δ_C($CDCl_3$ + DMSO) 27.25 (q, CH_3), 31.40 (q, CH_3), 100.24 (d, CH), 101.13 (s), 109.09 (s), 118.79 (s), 119.14 (d, CH), 121.35 (d, CH), 128.44 (d, CH), 140.28 (s), 141.80 (d, CH), 154.64 (s), 162.71 (s), 165.57 (s) and 187.09 (s); ν_{max}(KBr)/cm^{-1} 1650 (C=O) and 1600 (C=O) (Found: C, 53.0, H, 4.1; N, 10.7. $C_{17}H_{15}N_3O_4$ requires C, 53.04; H, 5.07; N, 10.03%).

Reaction of 1b with acetoacetamide. 6-*Carbamoyl*-7-*hydroxy*-1,3-*dimethylquinazoline*-2,4-*dione* **3h** (60%).—Mp 332–333 °C (EtOH); *m/z* 249 (M^+); δ_H($CDCl_3$ + TFA) 3.12 (3 H, s, NCH_3), 3.22 (3 H, s, NCH_3), 7.56 (1 H, s, 8-H) and 8.49 (1 H, s, 5-H); δ_C($CDCl_3$ + DMSO) 27.09 (q, CH_3), 31.22 (q, CH_3), 95.69 (s), 111.74 (d, CH), 121.19 (s), 146.76 (s), 147.32 (d, CH), 154.55 (s), 162.36 (s), 164.99 (s) and 190.69 (s); ν_{max}(KBr)/cm^{-1} 1660 (C=O) and 1610 (C=O) (Found: C, 40.7; H, 5.5; N, 12.4. $C_{11}H_{11}N_3O_4$ requires C, 41.04; H, 5.89; N, 13.23%).

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