Synthesis of 1*H*-Isoindoles by a Novel Rearrangement of Some Isoquinolin-4(1*H*)-ones

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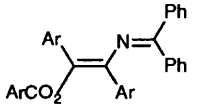
The isoquinolinones **8** undergo acid-induced rearrangement to yield the isomeric 1,1-dihydro-3-aroylisoindoles **9** in good yield. The reaction involves hydrolysis of the C=N bond to afford a putative intermediate amino diketone **10**. Cyclization within this is controlled by two factors (i) the stability of the C=N group in the starting material and product and (ii) the relative reactivity of the two carbonyl groups.

During a study [1] of the photochemical behaviour of a series of 2-aza-1,3-dienes we observed a dramatic influence of substitution on the outcome of the reaction. In the examples illustrated by compound **1** the reaction provided an efficient route to dihydrooxazoles **2**.[2] This process was interpreted as one



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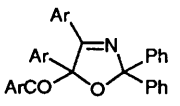

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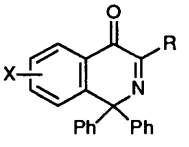
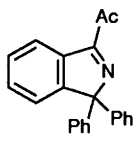


3 R = Ar
4 R = Me



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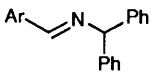
involving an electron transfer from the electron-rich imine system to the benzoyl group leading to a novel 1,2-migration of that group in a reaction akin to the oxa-di-π-methane process. One of the tests for the involvement of an electron transfer mechanism involved the protonation of the molecules **1** by perchloric acid. Under these conditions irradiation brought about a new reaction in which the 2-aza-1,3-dienes **1** were converted rapidly and efficiently into a series of isoquinolinones **3** by a photochemical Mannich cyclization.[3] Usually the isoquinolinones obtained were aryl substituted and stable. However, in one example an isoquinolinone **4** was prepared with a 2-methyl substituent. This substitution pattern apparently made the compound less stable and it rearranged readily under mild conditions, either in ethanol or in dilute sulfuric acid–THF, into the isoindole **5**.[3] While the synthesis of the isomeric 2*H*-isoindoles is well documented[4] there are fewer routes to the 1*H*-isoindoles particularly where isomerization to the 2*H*-isomers is not possible.[5] Furthermore, the substitution pattern illustrated by compound **5** has not been reported previously. This paper describes the reactions of other isoquinolin-4(1*H*)-ones establishing the scope of this new synthetic route to 1*H*-isoindoles.

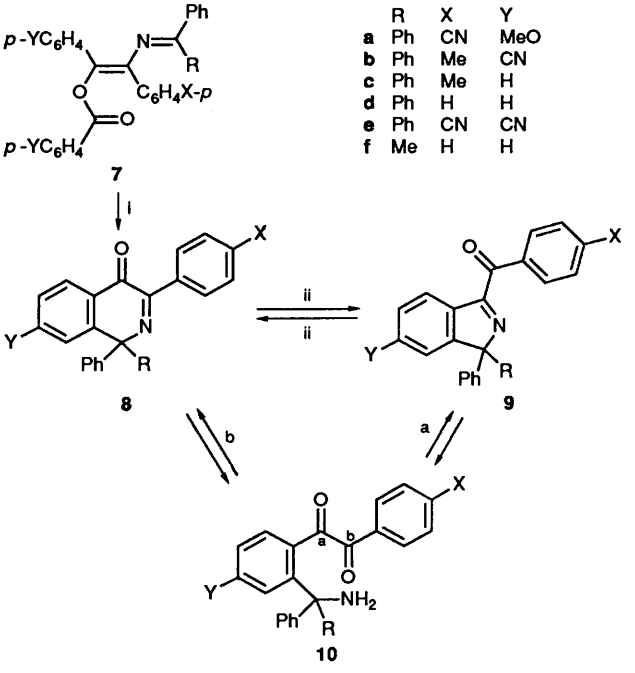
Results and Discussion

The isoquinolinones **8c–f** required for this study had been prepared by us at an earlier date.[2] In addition to these two new isoquinolinones **8a, b** were prepared by our earlier procedure involving the double aroylation of the anion generated from the



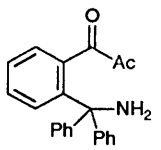
6a Ar = *p*-CNC_6H_4
b Ar = *p*-MeC_6H_4

imines **6**. By this route reasonable yields of the new azadienes **7a, b** were obtained and their identities authenticated by conventional methods. These compounds were then photocyclized by irradiation in the presence of perchloric acid to afford the new isoquinolinones **8a, b** in yields of 24 and 46% respectively (Scheme 1). The identity of these was readily established by standard techniques. The other isoquinolinones **6c–f** were obtained by the previously described route.[2]



Scheme 1 *Reagents and conditions:* i, *hv*, CH_2Cl_2, $HClO_4$; ii, H_2SO_4–H_2O (25%)–THF

As mentioned above the isoquinolinone **4** was thermally reactive and could be converted quantitatively into compound **5**. The mechanism proposed [2] for this involved hydrolysis of the imine double bond to afford an amino diketone **11**. Cyclization



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within this could either reform starting material or else afford the isoindole. The fact that only the isoindole was formed raised the question of what factors controlled the preference for formation of the five-membered ring. With regard to this Baldwin's rules[6] suggest that either mode of cyclization to the six- or five-membered ring would be allowed in a system of this sort. However, on a simple basis it could be suggested that the quantitative formation of the isoindole **5** was due to thermodynamic control since this isoindole has an imine system that is more stable than that in the isoquinolinone **4**. The stability of an imine towards hydrolysis depends to a great extent on the substituents attached to the group and alkyl imines undergo more facile hydrolysis than do aryl imines.[7] Thus, it was necessary to establish the factors controlling the cyclization.

The isoquinolinones **8** were all subjected to treatment in THF–water–sulfuric acid for 48 h. Conventional work-up afforded mixtures of the starting material and the corresponding isoindoles **9** (Table 1). Such a result is in contrast to that reported for the rearrangement of the isoquinolinone **4** where only the isoindole **5** is obtained.[2] As mentioned above the reason for this specificity could be the preferential stability of the imine moiety in compound **5** thus favouring the forward reaction, **4** to **5**, without the intervention of the reverse process. This is in complete contrast to the difference between the isoquinolinones **8** and the isoindoles **9** where the imine groups could be of equivalent stability. Therefore, other influences have to be considered in order to explain the non-quantitative conversion of **8** into **9**. A possible explanation could be that the rearrangements of **8** are kinetically controlled and are dependent on the relative reactivities of the two carbonyl groups 'a' and 'b' in the intermediate amino diketone **10** (Scheme 1). With isoquinolinones **8d–f**, where the keto groups in **10** have comparable substitution and reactivity, the yields of isoindole and recovered starting material are close to 1:1, showing that ring size has little effect on the equilibrium illustrated in the scheme. However, with the isoquinolinones **8b** and **8c** in which there is a marked difference between the reactivity of the two carbonyl groups, the more reactive keto group will be 'a', and cyclization with this affords an isoindole:isoquinolinone ratio of *ca.* 2. The last example, **8a**, reverses this situation and keto group 'b' is more reactive leading to an isoindole:isoquinolinone ratio of 0.2.

This study has shown that the thermal rearrangement of isoquinolinones to isoindoles under acidic conditions is quite general. The reaction involves hydrolysis and ring opening of the isoquinolinone to an amino 1,2-diketone followed by cyclization. The process is controlled by two factors namely the stability of the C=N group in both the starting material and product and the relative reactivity of the two carbonyl groups in the intermediate. When the isoindole has a C=N group that is more stable than that in the starting isoquinolinone then the reaction is dominated by formation of the isoindole. However, in other situations where the stability of C=N in the isoquinolinone and the isoindole are comparable the outcome of the rearrangment is dependent upon cyclization at the more reactive keto group in the amino diketone intermediate.

Table 1 Formation of compound **9**

9	Yield (%)	Ratio **9**:**8**
a	12	0.2
b	67	2.4
c	65	2.0
d	54	1.3
e	50	1.2
f	41	0.9

Experimental

M.p.s were determined on a Buchi 510D apparatus in open capillaries and are uncorrected. IR spectra were recorded as KBr discs using a Perkin-Elmer 257 spectrophotometer. NMR spectra were recorded in $CDCl_3$ solution using a Varian FT-300A for ^1H and ^{13}C spectra with chemical shifts δ expressed in ppm downfield from internal Me_4Si and coupling constants J are given in Hz. UV/VIS spectra were recorded in methylene dichloride solution using a Perkin-Elmer 550 spectrometer. Mass spectra were determined on a Varian MAT-711 spectrometer.

Synthesis of 2-Aza-1,3-dienes

The synthesis of the 2-aza-1,3-dienes **7c–f** has been reported previously by us.[2]

3-(p-*Cyanophenyl*)-4-(p-*methoxybenzoyloxy*)-4-(p-*methoxyphenyl*)-1,1-*diphenyl*-2-*azabuta*-1,3-*diene* **7a**.—This compound was prepared in the conventional manner[2] from *N*-diphenylmethyl-*p*-cyanophenylmethanimine **6a** (2.0 g, 6.76 mmol) in THF (5 cm^3), 4-methoxybenzoyl chloride (5.76 g, 33.8 mmol) in HMPA (60 cm^3) and sodium hydride (0.81 g, 33.8 mmol). Conventional work-up followed by chromatography on silica gel using hexane–diethyl ether (7:3) as eluent yielded the desired *diene* **7a** (1.53 g, 40%) as yellow crystals, m.p. 218–219 °C (from ethanol); ν_{max}/cm^{-1} 2240 (C≡N), 1740 (C=O) and 1615 (C=N); δ_H 7.9 (2 H, d, *J* 7, ArH), 7.8 (2 H, d, *J* 7, ArH), 7.5–7.1 (14 H, m, ArH), 6.9–6.8 (4 H, m, ArH), 3.83 (3 H, s, MeO) and 3.76 (3 H, s, MeO); δ_C 171.6 (C=N), 165.0 (CO_2), 163.8, 159.2, 143.4–109.8 (ArC), 113.6 (C≡N), 55.3 (MeO) and 55.0 (MeO); λ_{max}/nm 259 (ε=46 000 $dm^3\ mol^{-1}\ cm^{-1}$) and 330 (15000); *m/z* 564 (M^+, 20%), 429 (100), 294 (6), 273 (6), 165 (32) and 135 (44) (Found C, 78.6; H, 5.1; N, 4.8. $C_{37}H_{28}N_2O_4$ requires C, 78.72; H, 4.96; N, 4.96%).

4-(p-*Cyanobenzoyloxy*)-4-(p-*cyanophenyl*)-1,1-*diphenyl*-3-(p-*methylphenyl*)-2-*azabuta*-1-3-*diene* **7b**.—This compound was prepared in the conventional manner[2] from *N*-diphenylmethyl-*p*-methylphenylmethanimine **6b** (2.0 g, 7.02 mmol) in THF (5 cm^3), 4-cyanobenzoyl chloride (5.81 g, 35.1 mmol) in HMPA (60 cm^3) and sodium hydride (0.84 g, 35.1 mmol). Conventional work-up followed by chromatography on silica gel using hexane–diethyl ether (17:3) as eluent yielded the desired diene **7b** (2.93 g, 77%) as yellow crystals, m.p. 215–216 °C (from ethanol); ν_{max}/cm^{-1} 2250 (C≡N), 1750 (C=O) and 1605 (C=N); δ_H 8.1 (2 H, d, *J* 8, ArH), 7.9–6.7 (20 H, m, ArH) and 2.2 (3 H, s, Me); δ_C 171.0 (C=N), 163.6 (CO_2), 143.6–126.9 (ArC), 118.6 (C≡N), 117.5 (C≡N), 116.7, 109.9 and 21.0 (Me); λ_{max}/nm (ε) 244 (49 500) and 321 (21 000); *m/z* 543 (M^+, 14%), 413 (100), 283 (64), 165 (79) and 130 (14) (Found C, 81.2; H, 4.6; N, 7.5. $C_{37}H_{25}N_3O_2$ requires C, 81.77; H, 4.60; N, 7.73%).

Preparative Photolyses

The photolyses were carried out in an immersion well apparatus with a Pyrex filter and a 400 W medium pressure Hg arc lamp.

Solutions of the compounds in methylene dichloride (400 cm^3) were purged for 1 h with argon and irradiated under a positive pressure of argon for the times shown. After completion of the irradiation solid Na_2CO_3 was added to neutralize the perchloric acid. The photolysate was then filtered and the solvent was removed under reduced pressure. The residue was treated with water and extracted into chloroform. The organic layer washed with water, dried ($MgSO_4$), filtered and evaporated to dryness under reduced pressure. The resultant oil was separated by chromatography on a column of silica gel using hexane–ethyl acetate (4:1) as eluent.

3-(p-*Cyanophenyl*)-7-*methoxy*-1,1-*diphenylisoquinolin*-4-(1H)-*one* **8a**.—The diene **7a** (600 mg, 1.06 mmol) and perchloric acid (534 mg, 5.3 mmol) were irradiated for 30 min and Na_2CO_3 (560 mg, 5.3 mmol) was added. Conventional work-up afforded the *isoquinolinone* **8a** (110 mg, 24%) as yellow crystals, m.p. 162–164 °C (from ethanol); ν_{max}/cm^{-1} 2230 (C≡N), 1660 (C=O) and 1590 (C=N); δ_H 8.2 (1 H, d, *J* 9, ArH), 8.1 (2 H, d, *J* 8, ArH), 7.7 (2 H, d, *J* 8, ArH), 7.3–7.1 (10 H, m, ArH), 7.0 (1 H, dd, J_1 9, J_2 2, ArH), 6.7 (1 H, d, *J* 2, ArH) and 3.8 (3 H, s, MeO); δ_C 174.0 (C=O), 159.0 (C=N), 150.7, 144.6, 139.4, 132.7, 131.5–123.4, 118.6, 114.8, 114.5, 113.4 (ArC and C≡N), 72.5 (quaternary C) and 55.4 (MeO); *m*/*z* 428 (M^+, 38%), 411 (3), 300 (100), 268 (7), 257 (5), 239 (17), 165 (8), 128 (8) and 77 (6) (Found C, 81.1; H, 4.6; N, 6.5. $C_{29}H_{20}N_2O_2$ requires C, 81.31; H, 4.67; N, 6.54%).

7-*Cyano*-1,1-*diphenyl*-3-(p-*tolyl*)*isoquinolin*-4(1H)-*one* **8b**.—The diene **7b** (600 mg, 1.10 mmol) and perchloric acid (550 mg, 5.5 mmol) were irradiated for 35 min and Na_2CO_3 (580 mg, 5.5 mmol) was added. Conventional work-up afforded the *isoquinolinone* **8b** (210 mg, 46%) as yellow crystals, m.p. 190–191 °C (from ethanol); ν_{max}/cm^{-1} 2260 (C≡N), 1690 (C=O) and 1615 (C=N); δ_H 8.3 (1 H, d, *J* 8, ArH), 7.9 (2 H, d, *J* 8, ArH), 7.7 (1 H, dd, J_1 8, J_2 0.5, ArH), 7.6 (1 H, d, *J* 0.5, ArH), 7.4–7.3 (6 H, m, ArH), 7.2 (2 H, d, *J* 8, ArH), 7.2–7.1 (4 H, m, ArH) and 2.4 (3 H, s, Me); δ_C 174.9 (C=O), 159.6 (C=N), 148.9–117.6 (ArC), 115.7 (C≡N), 71.4 (quaternary C) and 21.3 (Me); *m*/*z* 412 (M^+, 15%), 295 (100), 266 (14), 218 (4), 190 (7), 165 (4) and 77 (2) (Found C, 84.2; H, 4.6; N, 7.0. $C_{29}H_{20}N_2O$ requires C, 84.47; H, 4.85; N, 6.80%).

Transformation of Isoquinolinones **8** *into Isoindoles* **9**

The corresponding isoquinolinone in THF was placed in a 100 cm^3 round-bottomed flask containing a magnetic stirring bar. Subsequently, H_2SO_4 (25% in water) was added at room temperature. The reaction mixture was stirred for 48 h and extracted five times with ether. The organic layers were resumed and washed with aqueous $NaHCO_3$ and water, dried ($MgSO_4$), filtered and evaporated to dryness under reduced pressure. The resultant oil was separated by chromatography on a column of silica gel using a mixture of toluene–hexane (4:1) as eluent.

3-(p-*Cyanobenzoyl*)-6-*methoxy*-1,1-*diphenyl*-1H-*isoindole* **9a**.—The isoquinolinone **8a** (90 mg, 0.21 mmol) and H_2SO_4 (20 cm^3) in THF (20 cm^3) were allowed to react for 48 h. Conventional work-up afforded the *isoquinolinone* **8a** (74 mg, 82%) and the *isoindole* **9a** (11 mg, 12%) as white crystals, m.p. 143–144 °C (from ethanol); ν_{max}/cm^{-1} 2220 (C≡N), 1670 (C=O) and 1600 (C=N); δ_H 8.3 (2 H, d, *J* 8, ArH), 7.9 (1 H, d, *J* 8, ArH), 7.7 (2 H, d, *J* 8, ArH), 7.2–7.1 (10 H, m, ArH), 7.0 (1 H, d, *J* 2, ArH), 6.9 (1 H, dd, J_1 8, J_2 2, ArH) and 3.8 (3 H, s, MeO); δ_C 188.9 (C=O), 165.1 (C=N), 161.2–110.8 (ArC and C≡N), 88.2 (quaternary C) and 55.6 (MeO); *m*/*z* 428 (M^+, 67%), 400 (3), 298 (100), 272 (45), 130 (63), 102 (15) and 77 (8) (Found C, 81.5; H, 4.5; N, 6.4. $C_{29}H_{20}N_2O_2$ requires C, 81.31; H, 4.67; N, 6.54%).

6-*Cyano*-1,1-*diphenyl*-3-(p-*toluoyl*)-1H-*isoindole* **9b**.—The isoquinolinone **8b** (350 mg, 0.85 mmol) and H_2SO_4 (20 cm^3) in THF (20 cm^3) were allowed to react for 48 h. Conventional work-up afforded the isoquinolinone **8b** (100 mg, 28%) and the *isoindole* **9b** (235 mg, 67%) as white crystals, m.p. 178–179 °C (from ethanol); ν_{max}/cm^{-1} 2250 (C≡N), 1660 (C=O) and 1615 (C=N); δ_H 8.2 (2 H, d, *J* 8, ArH), 8.1 (1 H, d, *J* 8, ArH), 7.9 (1 H, s, ArH), 7.3–7.1 (13 H, m, ArH) and 2.4 (3 H, s, Me); δ_C 188.8 (C=O), 165.1 (C=N), 156.1–118.4 (ArC), 112.6 (C≡N), 88.8 (quaternary C) and 21.8 (Me); *m*/*z* 412 (M^+, 73%), 397 (1), 384 (21), 335 (1), 293 (15), 190 (3), 165 (5), 119 (100), 91 (50) and 77 (5) (Found: C, 84.6; H, 4.6; N, 6.7. $C_{29}H_{20}N_2O$ requires C, 84.47; H, 4.85; N, 6.80%).

1,1-*Diphenyl*-3-(p-*toluoyl*)-1H-*isoindole* **9c**.—The isoquinolinone **8c** (150 mg, 0.39 mmol) and H_2SO_4 (15 cm^3) in THF (15 cm^3) were allowed to react for 48 h. Conventional work-up afforded the isoquinolinone **8c** (48 mg, 32%) and the *isoindole* **9c** (98 mg, 65%) as white crystals, m.p. 117–118 °C (from ethanol); ν_{max}/cm^{-1} 1650 (C=O) and 1605 (C=N); δ_H 8.2–7.0 (18 H, m, ArH) and 2.4 (3 H, s, Me); δ_C 190.1 (C=O), 166.8 (C=N), 155.8–124.2 (ArC), 88.4 (quaternary C) and 21.6 (Me); *m*/*z* 387 (M^+, 25%), 359 (3), 268 (8), 119 (100), 105 (10), 91 (32) and 77 (17) (Found: C, 86.6; H, 5.3; N, 3.8. $C_{28}H_{21}NO$ requires C, 86.82; H, 5.42; N, 3.61%).

3-*Benzoyl*-1,1-*diphenyl*-1H-*isoindole* **9d**.—The isoquinolinone **8d** (80 mg, 0.21 mmol) and H_2SO_4 (10 cm^3) in THF (10 cm^3) were allowed to react for 48 h. Conventional work-up afforded the isoquinolinone **8d** (32 mg, 41%) and the *isoindole* **9d** (42 mg, 54%) as white crystals, m.p. 118–119 °C (from ethanol); ν_{max}/cm^{-1} 1670 (C=O) and 1605 (C=N); δ_H 8.3–7.1 (m, ArH); δ_C 190.5 (C=O), 166.6 (C=N), 155.9–124.3 (ArC) and 88.5 (quaternary C); *m*/*z* 373 (M^+, 100%), 345 (23), 296 (9), 268 (71) and 105 (23) (Found: C, 86.7; H, 4.9; N, 3.6. $C_{27}H_{19}NO$ requires C, 86.86; H, 5.09; N, 3.75%).

6-*Cyano*-3-(p-*cyanobenzoyl*)-1,1-*diphenyl*-1H-*isoindole* **9e**.—The isoquinolinone **8e** (60 mg, 0.14 mmol) and H_2SO_4 (10 cm^3) in THF (10 cm) were allowed to react for 48 h. Conventional work-up afforded the isoquinolinone **8e** (27 mg, 43%) and the *isoindole* **9e** (29 mg, 50%) as white crystals, m.p. 226–227 °C (from ethanol); ν_{max}/cm^{-1} 2250 (C≡N), 1680 (C=O) and 1610 (C=N); δ_H 8.4 (2 H, d, *J* 8, ArH), 8.3 (1 H, d, *J* 8, ArH), 7.9 (1 H, s, ArH), 7.8 (3 H, d, *J* 8, ArH) and 7.4–7.2 (10 H, m, ArH); δ_C 187.8 (C=O), 164.2 (C=N), 156.3–125.7 (ArC), 116.9 (C≡N), 113.1 (C≡N) and 89.3 (quaternary C); *m*/*z* 423 (M^+, 85%), 395 (2), 321 (2), 293 (100), 277 (15), 264 (7), 215 (10), 130 (50) and 102 (24) (Found: C, 82.4; H, 3.9; N, 9.9. $C_{29}H_{17}N_3O$ requires C, 82.27; H, 4.02; N, 9.93%).

3-*Benzoyl*-1-*methyl*-1-*phenyl*-1H-*isoindole* **9f**.—The isoquinolinone **8f** (220 mg, 0.71 mmol) and H_2SO_4 (15 cm^3) in THF (15 cm^3) were allowed to react for 48 h. Conventional work-up afforded the isoquinolinone **8f** (106 mg, 48%) and the *isoindole* **9f** (90 mg, 41%) as white crystals, m.p. 103–104 °C (from ethanol); ν_{max}/cm^{-1} 1680 (C=O) and 1615 (C=N); δ_H 8.3 (2 H, d, *J* 7, ArH), 7.9 (1 H, m, ArH), 7.6–7.2 (11 H, m, ArH) and 2.0 (3 H, s, Me); δ_C 190.7 (C=O), 166.0 (C=N), 158.2–122.4 (ArC), 81.6 (quaternary C) and 25.0 (Me); *m*/*z* 311 (M^+, 41%), 296 (2), 283 (7), 206 (100), 180 (15), 105 (54) and 77 (23) (Found: C, 84.7; H, 5.7; N, 4.3. $C_{22}H_{17}NO$ requires C, 84.89; H, 5.47; N, 4.50%).

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