Direct Arylation of Nitrobenzenes and of Heterocycles *via* an Oxygen Analogue of the Benzidine Rearrangement

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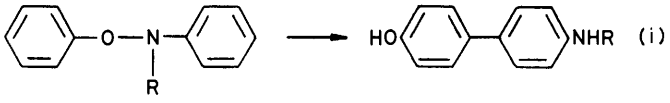
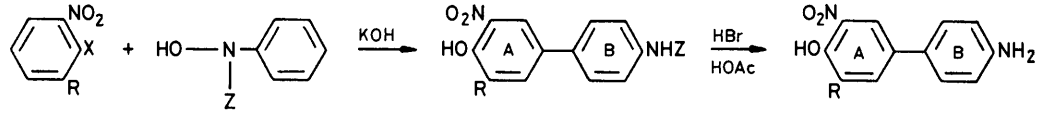
Benzyl *N*-hydroxy-*N*-phenylcarbamate (1) and *N*-phenylbenzohydroxamic acid (10) react with active halogenobenzenes to give derivatives of 4-amino-4'-hydroxybiphenyl. The reactions of compound (1) or (10) with certain 2-chloro-pyridines, -pyrimidines, and -pyrazines result in introduction of the 4-aminophenyl group at position 5 of the heterocycle. The scope and limitations of the reaction are discussed.

THE 'oxa-benzidine'† rearrangement (i) was predicted by Dewar in 1963,[1] but its occurrence has not yet been demonstrated directly. However, as three different



reactions which should have produced *NO*-diarylhydroxylamines are reported to give 4-amino-4'-hydroxybiphenyls,[2-4] it can be assumed that this rearrangement indeed occurs.

The rearrangement differs from the benzidine rearrangement in several respects, the most important being that it proceeds (i) under basic conditions and (ii) in systems which carry electron-withdrawing groups. Although the exact mechanism is still unclear,[5] this reaction can provide an excellent means of forming aryl–aryl bonds. For this purpose we have now carried out the rearrangement intentionally and explored its synthetic potential.

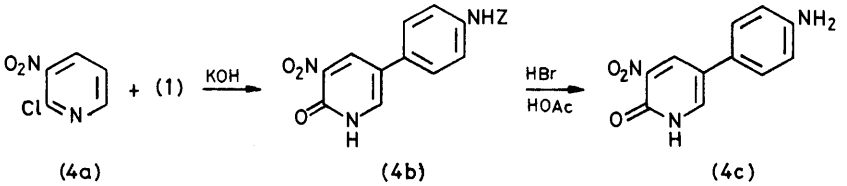


(2a) X = F, R = H (1) (2b) R = H (2c) R = H
(3a) X = Cl, R = NO_2 (3b) R = NO_2 (3c) R = NO_2

Z = $PhCH_2 \cdot O \cdot CO$

The simplest route to the intermediate *NO*-diarylhydroxylamines was considered to be the reaction of salts of *N*-arylhydroxamic acids with reactive halogenobenzenes. The hydroxamic acid selected was benzyl *N*-hydroxy-*N*-phenylcarbamate (1), as its *N*-acyl group can be removed easily. Compound (1) in ethanolic potassium hydroxide reacted with 1-fluoro-2-nitrobenzene (2a) to give 4'-benzyloxycarbonylamino-4-hydroxy-3-nitrobiphenyl (2b) in 75% yield. Treatment of this product (2b) with hydrogen bromide in acetic acid gave the amine (2c) quantitatively. In the same manner the carbamate (1) reacted readily with 1-chloro-2,6-dinitrobenzene (3a) to give (72%) the biphenyl (3b), which was transformed into (3c).

The identification of the products as biphenyls rather than hydroxylamines is based on spectral evidence. The n.m.r. spectra reveal (Table 1) one 1,4-disubstituted ring in all compounds [4 H singlet for (2b) and (3b) and a pair of doublets for (2c) and (3c)], a 1,3,4-trisubstituted ring in (2b) and (2c) (two doublets and a doublet of doublets with the typical *ortho* and *meta* splittings), and a 1,3,4,5-tetrasubstituted ring in (3b) and (3c) (2 H low-field singlet). The i.r. spectra confirm these assignments and indicate the presence of OH, NH, or NH_2 groups. A careful search failed to detect any other isomers.



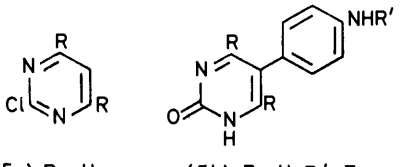
(4a) (4b) (4c)

The success in preparative arylation of nitrobenzenes led us to try to utilize the method for direct arylation of heterocyclic systems. The reaction of the carbamate (1) with 2-chloro-3-nitropyridine (4a) proceeded in 85% yield, and the spectra of the product clearly indicate that the pyridine ring was arylated at position 5 to give the

† Strictly speaking this use of the term 'oxa-benzidine' is incorrect, since the prefix 'oxa' means replacement of a *carbon* by an oxygen atom.

[1] M. J. S. Dewar in 'Molecular Rearrangements,' vol. I, ed. P. DeMayo, Interscience, New York and London, 1963, p. 344.
[2] J. R. Cox and M. F. Dunn, *Tetrahedron Letters*, 1963, 985.
[3] K. B. Shaw and R. K. Miller, *Canad. J. Chem.*, 1970, **48**, 1394.
[4] T. Sheradsky and G. Salemnick, *Tetrahedron Letters*, 1971, 645.
[5] T. Sheradsky and G. Salemnick, *Israel J. Chem.*, 1972, **10**, 857.

pyridone (4b). Treatment of the product (4b) with hydrogen bromide in acetic acid furnished the amine (4c). Similarly 2-chloropyrimidine (5a) and its 4,6-dimethyl derivative (6a) were converted into the 5-arylpyrimidones (6c) (58%) and (7c) (38%), respectively.

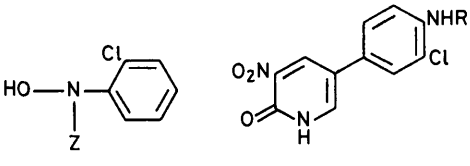


(5a) R = H
(6a) R = Me

(5b) R = H, R' = Z
(5c) R = H, R' = H
(6b) R = Me, R' = Z
(6c) R = Me, R' = H

Comparison of the spectra of compounds (5) and (6) confirms that the methyl groups in (6c) and (6b) hinder free rotation around the inter-ring bond and cause deviation from planarity. The u.v. absorptions of compounds (6b and c) appear at shorter wavelengths ($\Delta\lambda$ 30—50 nm) than those of (5b and c). In the n.m.r. spectra

However, the *para*-positions of both rings have to be unsubstituted carbon atoms. When either of these positions is substituted or is a nitrogen atom, complex



(9)

(8b) R = Z
(8c) R = H

mixtures are produced. The mixtures contain products of *ortho*-rearrangements, diaryl ethers, and cleavage products.[5]

An important factor in the reactions described is the amount of alkali used, and that depends on the relative acidity of the reagent (1) and the products. Compounds (2b), (3b), (4b), and (8b) are more acidic than (1) and thus form alkali salts as soon as they are produced. In these cases 2 equiv. of potassium hydroxide are required to bring the reaction to completion, and the

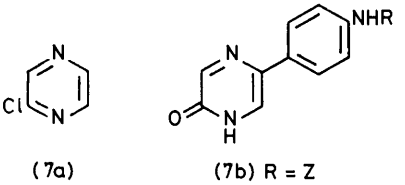
TABLE 1

^{1}H N.m.r. data for 4'-amino-4-hydroxybiphenyls (δ values; J in Hz)

	Ring A				
Compd.	H-2	H-6	H-5	Ring B	Others
(2b)	8.19 (d) $J_{2,6}$ 2.5, $J_{5,6}$ 9	7.85 (dd)	7.28 (d)	7.58 (4 H, s)	5.17 (2 H, s) 7.40 (5 H, s)
(2c)	8.03 (d) $J_{2,6}$ 2.5, $J_{5,6}$ 9	7.77 (dd)	7.18 (d)	7.28 (2 H, d), 6.68 (2 H, d) J 8	
(3b)	8.47 (2 H, s)			7.67 (4 H, s)	5.18 (2 H, s) 7.42 (5 H, s)
(3c)	8.38 (2 H, s)			7.58 (2 H, d), 6.85 (2 H, d) J 8	

the *ortho*-protons of the phenyl ring of (6c) resonate at higher field than those of (5c) ($\Delta\delta$ 0.5 p.p.m.). The methyl signals appear at δ 1.95—1.98, *i.e.* at much higher field than is usual for methylpyrimidines.[6]

2-Chloropyrazine (7a) was also transformed, by the same two steps, into 5-(4-aminophenyl)pyrazin-2-one (7c) (45%).



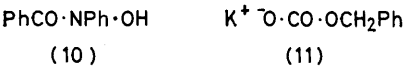
(7a)

(7b) R = Z
(7c) R = H

Reactions of the halides (2a), (3a), (4a), and (5a) with *N*-phenylbenzohydroxamic acid (10) proceeded in similar yields, and resulted in smooth introduction of the 4-benzoylaminophenyl group at the appropriate positions.

The aryl group introduced can carry additional substituents. For example benzyl *N*-(2-chlorophenyl)-*N*-hydroxycarbamate (9) also reacted with the chloropyridine (4a), to give the 5-arylpyridone (8c) in 72% yield.

products are first isolated as potassium salts. Compounds (5b), (6b), and (7b), on the other hand, are less acidic than (1), and only 1 equiv. of potassium hydroxide is required. The presence of a second mol. equiv. in these cases lowers the yields considerably. Another factor is the reactivity of the halogen. Salts of *N*-arylhydroxamic acids and *N*-hydroxycarbamates decompose slowly in solution [7] and in order to achieve arylation the reaction has to be fast. In this work yields were seen to diminish as the halogen reactivity became lower and the



(10)

(11)

reaction slower. No arylation product was formed on treating the carbamate (1) with 2-chloro- or 2-fluoropyridine; only potassium benzyl carbonate (11) precipitated out. The reagent (10) yielded only potassium benzoate.

EXPERIMENTAL

Caution: In view of the possible carcinogenic nature of some of the compounds described below, appropriate care in handling should be taken.

M.p.s were determined with a Thomas–Hoover apparatus.

[6] T. J. Batterham, D. J. Brown, and M. N. Paddon-Row, *J. Chem. Soc.* (*B*), 1967, 171.

[7] E. Boyland and R. Nery, *J. Chem. Soc.* (*C*), 1966, 346.

Spectra were recorded as follows; n.m.r. for solutions in $(CD_3)_2SO$ (Varian T-60 or EM-360 instrument); u.v. for solutions in ethanol (Unicam SP 800); i.r. for Nujol mulls or KBr pellets (Perkin-Elmer 257).

Reaction of 1-*Fluoro*-2-*nitrobenzene* (2a) *with Benzyl* N-*Hydroxy*-N-*phenylcarbamate* (1).—To a solution of the carbamate (1) [7] (1.22 g, 5 mmol) in ethanolic potassium hydroxide (0.5N; 40 ml), 1-fluoro- 2-nitrobenzene (0.7 g, 5 mmol) in ethanol (5 ml) was added with shaking, and the solution was left at room temperature. A red precipitate began to form after 5 min and was filtered off after 4 h. It was suspended in dilute acetic acid, in which it turned yellow, was filtered off again, and crystallized from ethyl acetate to give 4′-*benzyloxycarbonylamino*-4-*hydroxy*-3-*nitrobiphenyl* (2b) as yellow plates (1.42 g, 75%), m.p. 172—173°, $\lambda_{max.}$ 277 (log ε 4.59) and 387 nm (3.26), $\nu_{max.}$ 3 330 (NH) and 1 700 cm^{-1} (C=O) (Found: C, 66.3; H, 4.5; N, 7.7 $C_{20}H_{16}NO_5$ requires C, 65.9; H, 4.4; N, 7.7%).

Compound (2b) (0.38 g) dissolved in 2N-hydrogen bromide in acetic acid (10 ml) was heated under reflux for 20 min, during which time a colourless solid precipitated. The solid was separated and suspended in sodium hydrogen carbonate solution, in which it turned dark-red. It was then suspended in dilute acetic acid and turned orange-red. Crystallization from n-butanol afforded 4′-*amino*-4-*hydroxy*-3-*nitrobiphenyl* as orange-red crystals (0.22 g), m.p. 135—136°, $\lambda_{max.}$ 284 (log ε 4.34) and 410 nm (3.10), $\nu_{max.}$ 3 475 and 3 380 cm^{-1} (Found: C, 62.6; H, 4.3; N, 12.2. $C_{12}H_{10}N_2O_3$ requires C, 62.6; H, 4.4; N, 12.2%).

Reaction of the Carbamate (1) *with* 1-*Chloro*-2,6-*dinitrobenzene* (3a).—This was carried out and proceeded in the same manner as the reaction with (2a) [1.01 g (5 mmol) of (3a)]. 4′-*Benzyloxycarbonylamino*-4-*hydroxy*-3,5-*dinitrobiphenyl* (3b) was obtained as orange-red needles (1.48 g, 72%), m.p. 188°, $\lambda_{max.}$ 288 (log ε 4.53) and 393 nm (3.26), $\nu_{max.}$ 3 410 (NH) and 1 725 cm^{-1} (C=O) (Found: C, 58.8; H, 3.55; N, 10.2. $C_{20}H_{15}N_3O_7$ requires C, 58.7; H, 3.7; N, 10.3%).

Treatment of the product (3b) (0.4 g) with hydrogen bromide in acetic acid, as above, yielded 4′-*amino*-4-*hydroxy*-3,5-*dinitrobiphenyl* (3c) (0.27 g) as orange crystals, m.p. 220—221°, $\lambda_{max.}$ 291 (log ε 4.32) and 402 nm (3.04), $\nu_{max.}$ 3 430 and 3 290 cm^{-1} (Found: C, 52.2; H, 3.4; N, 15.1. $C_{12}H_{19}N_3O_5$ requires C, 52.5; H, 3.3; N, 15.3%).

Reactions of the Carbamates (1) *and* (9) *with* 2-*Chloro*-3-*nitropyridine* (4a).—To a solution of the carbamate (1) (1.22 g, 5 mmol) in ethanolic potassium hydroxide (1N; 20 ml), a solution of 2-chloro-3-nitropyridine (4a) (0.8 g, 5 mmol) in ethanol (20 ml) was added. After 30 min the red precipitate was collected, stirred in dilute acetic acid, in which it changed colour to orange-yellow, filtered off, and crystallized from ethyl acetate to give 5-(4-*benzyloxycarbonylaminophenyl*)-3-*nitro*-2-*pyridone* (4b) (1.55 g), m.p. 251—252°, $\lambda_{max.}$ 279 (log ε 4.51) and 398 nm (3.65), $\nu_{max.}$ 3 310 and 3 260 (NH), and 1 690 cm^{-1} (C=O) (Found: C, 62.25; H, 4.1; N, 11.8. $C_{19}H_{15}N_3O_5$ requires C, 62.5; H, 4.1; N, 11.5%).

Treatment of the product (4b) (0.365 g) with hydrogen bromide in acetic acid as above gave 5-(4-*aminophenyl*)-3-*nitro*-2-*pyridone* (4c) as orange-red crystals (0.22 g), m.p. 297—300°, $\lambda_{max.}$ 284 (log ε 4.42) and 415 nm (3.48), $\nu_{max.}$ 3 440, 3 415, and 3 350 cm^{-1} (Found: C, 57.3; H, 4.0; N, 17.8. $C_{11}H_9N_3O_3$ requires C, 57.1; H, 3.9; N, 18.2%).

In the same manner compounds (4a) and (9) yielded 5-(4-*benzyloxycarbonylamino*-3-*chlorophenyl*)-3-*nitro*-2-*pyridone* (8b) as orange crystals (77%), m.p. 220°, $\lambda_{max.}$ 278 (log ε 4.21) and 393 nm (3.48) (Found: C, 57.6; H, 3.5; N, 10.2. $C_{19}H_{14}ClN_3O_5$ requires C, 57.1; H, 3.5; N, 10.5%), which was converted quantitatively into 5-(4-*amino*-3-*chlorophenyl*)-3-*nitro*-2-*pyridone* (8c) as orange-red crystals, m.p. 259—261°, $\lambda_{max.}$ 284 (log ε 4.48) and 410 nm (3.61) (Found: C, 50.1; H, 3.3; N, 15.5. $C_{11}H_8ClN_3O_3$ requires C, 49.7; H, 3.0; N, 15.8%).

TABLE 2

^1H N.m.r. data for 5-(4-aminophenyl) heterocycles (δ values; J in Hz)

Compd.	Heterocycle	Aryl	Others
(4b)	8.72 (1 H, d, H-4) 8.18 (1 H, d, H-6) J 3.5	7.57 (4 H, s)	5.20 (2 H, s) 5.40 (5 H, s)
(4c)	8.50 (1 H, d, H-4) 7.75 (1 H, d, H-6) J 2.5	7.22 (2 H, d) 6.65 (2 H, d) J 8	
(5b)	8.62 (2 H, s, H-4 and -6)	7.53 (4 H, s)	5.18 (2 H, s) 7.42 (5 H, s)
(5c)	8.50 (2 H, s, H-4 and -6)	7.33 (2 H, d) 6.68 (2 H, d) J 8	
(6b)		7.57 (2 H, d) 7.13 (2 H, d) J 8	5.20 (2 H, s) 7.40 (5 H, s) 1.95 (6 H, s)
(6c)		6.83 (2 H, d) 6.58 (2 H, d) J 8	1.98 (6 H, s)
(7b)	8.10 (1 H, d, H-3) 8.00 (1 H, d, H-6) J 0.7	7.83 (2 H, d) 7.53 (2 H, d) J 8	5.17 (2 H, s) 7.38 (5 H, s)
(7c)	8.08 (1 H, d, H-3) 7.87 (1 H, d, H-6) J 0.7	7.58 (2 H, d) 6.63 (2 H, d) J 8	
(8c)	8.63 (1 H, d, H-4) 8.10 (1 H, d, H-6) J 3	7.57 (1 H, d, H-2) 7.35 (1 H, dd, H-6) 6.87 (1 H, d, H-5) $J_{2,6}$ 2.5 $J_{5,6}$ 8	

Reaction of 2-*Chloropyrimidine with the Carbamate* (1).—To a solution of the carbamate (1) (1.22 g, 5 mmol) in ethanolic potassium hydroxide (0.25N; 20 ml), 2-chloropyrimidine (0.57 g, 5 mmol) in ethanol (20 ml) was added, and the solution was left at room temperature for 48 h. The precipitate was filtered off, suspended in dilute acetic acid, collected, and crystallized from dimethylformamide–water to give 5-(4-*benzyloxycarbonylaminophenyl*)-2-*pyrimidone* (5b) as pale yellow plates (0.93 g, 58%), m.p. 285—287°, $\lambda_{max.}$ 273 (log ε 4.53) and 337 nm (3.24), $\nu_{max.}$ 3 230 and 3 180 (NH) and 1 715 cm^{-1} (C=O) (Found: C, 67.0; H, 4.7; N, 13.4. $C_{18}H_{15}N_3O_3$ requires C, 67.3; H, 4.7; N, 13.1%).

Compound (5b) (0.32 g) in 2N-hydrogen bromide in acetic acid (10 ml) was heated under reflux for 30 min. The precipitate was filtered off and dissolved in aqueous sodium

hydrogen carbonate. 5-(4-*Aminophenyl*)-2-*pyrimidone* (5c) (0.15 g) was slowly precipitated as yellow needles, m.p. 266—268°, $\lambda_{max.}$ 282 (log ε 4.24) and 354 nm (3.20), $\nu_{max.}$ 3 405, 3 340, and 3 320 cm^{-1} (Found: C, 64.0; H, 4.95; N, 22.0. $C_{10}H_9N_3O$ requires C, 64.1; H, 4.85; N, 22.45%).

Reactions of the Carbamate (1) *with* 2-*Chloro*-4,6-*dimethylpyrimidine* (6a) *and with* 2-*Chloropyrazine* (7a).—These were carried out as for the reaction with (5a) to give 5-(4-*benzyloxycarbonylaminophenyl*)-4,6-*dimethyl*-2-*pyrimidone* (6b), pale yellow crystals, m.p. 263—265°, $\lambda_{max.}$ 248 (log ε 4.45) and 313 nm (3.70), $\nu_{max.}$ 3 270 (NH) and 1 740 cm^{-1} (C=O) (Found: C, 65.4; H, 5.5; N, 11.6. $C_{20}H_{19}N_3O_5$, H_2O requires C, 65.4; H, 5.8; N, 11.4%); 5-(4-*aminophenyl*)-4,6-*dimethyl*-2-*pyrimidone* (6c), yellow needles, m.p. 292—293°, $\lambda_{max.}$ 254 (log ε 4.16) and 296 nm (3.75), $\nu_{max.}$ 3 465, 3 370, and 3 235 cm^{-1} (Found: C, 61.7; H, 6.7; N, 17.8. $C_{12}H_{13}N_3O,H_2O$ requires C, 61.8; H, 6.5; N, 18.0%); 5-(4-*benzyloxycarbonylaminophenyl*)*pyrazin*-2-*one* (7b), pale yellow, m.p. 246—247°, $\lambda_{max.}$ 283 (log ε 4.46) and 354 nm (3.60), $\nu_{max.}$ 3 280 (NH) and 1 705 cm^{-1} (C=O) (Found: C, 67.1; H, 4.7; N, 12.8. $C_{18}H_{15}N_3O_3$ requires C, 67.3; H, 4.7; N, 13.1%); and 5-(4-*aminophenyl*)*pyrazin*-2-*one* (7c), yellow, m.p. 272—275° (decomp.), $\lambda_{max.}$ 294 (log ε 4.32) and 367 nm (3.43), $\nu_{max.}$ 3 420, 3 320, and 3 210 cm^{-1} (Found: C, 63.9; H, 4.9; N, 22.2. $C_{10}H_9N_3O$ requires C, 64.2; H, 4.85; N, 22.45%).

Reactions of Halides with N-*Phenylbenzohydroxamic Acid* (10).—These were carried out exactly as the corresponding reactions with the carbamate (1) to give 4′-*benzoylamino*-4-*hydroxy*-3-*nitrobiphenyl* [78% from (10) and (2a)] as yellow plates, m.p. 219—220° (from ethyl acetate), $\nu_{max.}$ 3 340 (NH) and 1 650 cm^{-1} (C=O) (Found: C, 68.3; H, 4.0; N, 8.1. $C_{19}H_{14}N_2O_4$ requires C, 68.3; H, 4.2; N, 8.4%); 4′-*benzoylamino*-4-*hydroxy*-3,5-*dinitrobiphenyl*, orange needles (82%), m.p. 239° (from ethyl acetate), $\nu_{max.}$ 3 400 (NH) and 1 670 cm^{-1} (C=O) (Found: C, 60.35; H, 3.8; N, 11.0. $C_{19}H_{13}N_3O_6$ requires C, 60.2; H, 3.45; N, 11.1%); 5-(4-*benzoylaminophenyl*)-3-*nitro*-2-*pyridone*, yellow crystals (78%), m.p. 322° (from dimethylformamide), $\nu_{max.}$ 3 340 (NH) and 1 680 cm^{-1} (C=O) (Found: C, 64.4; H, 4.2; N, 12.8. $C_{18}H_{13}N_3O_4$ requires C, 64.5; H, 3.9; N, 12.5%); and 5-(4-*benzoylaminophenyl*)-2-*pyrimidone*, pale yellow crystals (62%), m.p. 314° (from dimethylformamide), $\nu_{max.}$ 3 355 (NH) and 1 650 cm^{-1} (C=O) (Found: C, 69.7; H, 4.95; N, 14.6. $C_{17}H_{13}N_3O_2$ requires C, 70.1; H, 4.5; N, 14.4%).

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