A New Synthesis of 4*H*-1,3,4-Benzoxadiazines

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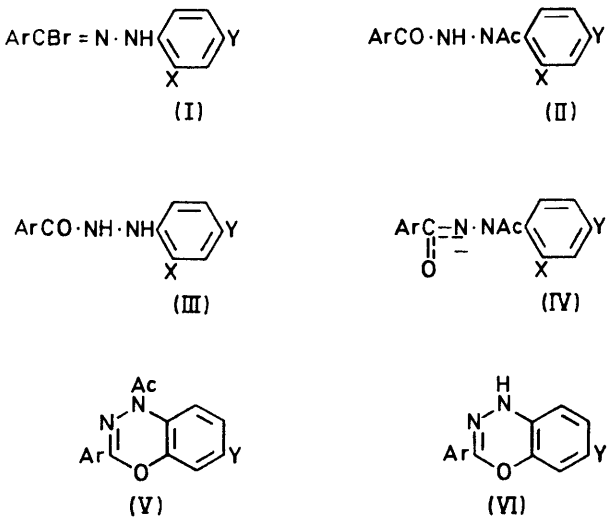
A synthesis of 4*H*-1,3,4-benzoxadiazines [(V) and (VI)] from *N*-aroyl-*N'*-acetyl-*N'*-(2,4-dihalogenophenyl)-hydrazines is described. The process involves displacement of *ortho*-halogen, fluorine being more readily displaced than bromine; in some cases a smooth deacetylation [(V) ⟶ (VI)] follows ring closure. A synthesis of a 7-nitro-4*H*-1,3,4-benzoxadiazine from a hydrazonyl bromide is reported.

We have been interested in generalizing the approaches used in 4*H*-1,3,4-benzothiadiazine synthesis [1] by developing a synthesis of compounds such as (V) and (VI) from appropriately substituted *N*-aroyl-*N'*-arylhydrazines such as (II) (see Scheme). The present work stems from the observation that, atypically, the hydrazide (IIIa) was isolated from reaction of the corresponding hydrazonyl bromide (Ia) with anhydrous sodium acetate in acetic acid; such reactions normally lead to the *N'*-acetyl derivative (II), probably *via* the hydrazonyl acetate as intermediate: [2]

$$ArCBr{=}N{\cdot}NHAr' \longrightarrow ArC(OAc){=}N{\cdot}NHAr' \longrightarrow ArCO{\cdot}NH{\cdot}NAcAr'$$

Since acetyl loss in this case was probably associated with poor nucleophilicity of N', conditions of acetolysis of the related compound (Ib) were modified by using dimethylformamide as solvent. Under these conditions, *O* ⟶ *N*-acetyl transfer readily occurred, but was accompanied by a ring closure involving displacement



a; Ar = Ph, X = Br, Y = CO_2Et
b; Ar = Ph, X = Br, Y = NO_2
c; Ar = Ph, X = Y = Br
d; Ar = Ph, X = F, Y = Br
e; Ar = p-ClC_6H_4, X = Y = Br
f; Ar = p-$MeO{\cdot}C_6H_4$, X = Y = Br
g; Ar = 5-Br-2-thienyl, X = Y = Br

Scheme

of the *ortho*-bromine atom to give the oxadiazine, *i.e.* (Ib) ⟶ (Vb).

The conversion of the hydrazide (IIc) into a benzoxadiazine with dimethylformamide as solvent and triethylamine as base was attempted without success. However, ring closure was accomplished in dimethylformamide–triethylamine with added sodium hydroxide to give the benzoxadiazine (VIc); the latter could readily be acetylated to give (Vc). The structures assigned to these compounds are substantiated by their ^1H n.m.r. spectra. In compound (VIc), the 5-proton gives rise to a high-field doublet in the aromatic region; in the spectrum of compound (Vc), this signal has moved considerably downfield under the influence of the neighbouring acetyl group. Since this proton shows only *ortho*-coupling, the bromine substituent must occupy the 7-position as shown.

The relationship between compounds (IIc), (Vc), and (VIc) follows from the observations that (Vc) can be smoothly deacetylated to (VIc), but that (IIIc) is not converted to (VIc) under the conditions for the conversion of (IIc) to (VIc). It may thus be inferred that ring closure precedes deacetylation in this process. In the case of the related hydrazide (IId), in which the displaceable halogen was fluorine, reaction occurred readily in dimethylformamide–triethylamine without added sodium hydroxide to give (Vc) in 93% yield.

Comparison between (IIc) and (IId) suggests that these cyclisation reactions, though requiring more forcing conditions than parallel syntheses of 4*H*-1,3,4-benzothiadiazines,[1] exhibit similar characteristics of nucleophilic aromatic substitution rather than those of an aryne mechanism.[3] Ring closure probably proceeds *via* the anion (IV) and involves attack by a negatively charged oxygen atom at the substituted *ortho*-position of the *N*-aryl ring. Since this aromatic ring is not formally activated towards such attack, cyclisation may proceed through a conjugate acid of (IV) bearing a positive charge on *N'*, though the concentration of such a species in the reaction medium would be small.

For further experiments, the hydrazonyl bromides (Ie, f, and g) were prepared by the standard method of brominating the aldehyde phenylhydrazone. In the case of thiophen-2-carbaldehyde phenylhydrazone, the heterocyclic ring was also substituted in this process. The ^1H n.m.r. spectrum of the derived hydrazonyl bromide showed an AB quartet for the thiophen ring protons (J 4·0 Hz) consistent only with β,β'-coupling.[4]

[1] (*a*) I. T. Barnish and M. S. Gibson, *J. Chem. Soc.* (*C*), 1970, 854; (*b*) P. D. Callaghan and M. S. Gibson, *ibid.*, p. 2106.
[2] J. M. Burgess and M. S. Gibson, *J. Chem. Soc.*, 1964, 1500.
[3] R. W. Hoffmann, 'Dehydrobenzene and Cycloalkynes,' Academic Press, New York and London, 1967, ch. 1.
[4] R. A. Hoffman and S. Gronowitz, *Arkiv Kemi*, 1960, **16**, 563.

An alternative synthesis from 5-bromothiophen-2-carbaldehyde confirmed the structure (Ig). These hydrazonyl bromides were converted into the respective hydrazides (II) in the normal way.

When treated with sodium hydroxide in dimethylformamide–triethylamine, as for the conversion of (IIc) to (VIc), compound (IIe) gave (VIe), loss of the acetyl group presumably occurring after ring closure. In contrast, (IIf) gave (Vf) and (IIg) gave (Vg), the acetyl group being retained even under the basic conditions. A separate attempt to remove the acetyl group from (Vf) under acidic conditions resulted in decomposition, although these conditions suffice for similar benzothiadiazines.[1a]

The direct and ready conversion of (Ib) to (Vb) by reaction with anhydrous sodium acetate in dimethylformamide has already been mentioned. The sequence would appear to be (Ib) ⟶ (IIb) ⟶ (Vb), although an attempt to identify (IIb) as an intermediate by interrupting the reaction was unsuccessful; only an artefact, apparently resulting from solvolysis of (Ib) by ethanol under the conditions of work-up,[5] was isolated:

$$ArCBr{=}N{\cdot}NHAr' \longrightarrow ArC(OEt){=}N{\cdot}NHAr'$$

Previously, 4*H*-1,3,4-benzoxadiazines have been available through the method of Huisgen and Fleischmann.[6] The present work provides a new, convenient, and potentially versatile synthesis from readily accessible materials.

EXPERIMENTAL

^{1}H N.m.r. spectra were recorded on Varian HA-100, A-60, and T-60 spectrometers (tetramethylsilane as internal standard). Unless otherwise stated, data refer to 60 MHz spectra. The presence of exchangeable protons (NH) was confirmed by use of deuterium oxide. Mass spectra were determined on a Hitachi–Perkin-Elmer RMU-6A spectrometer and also on a C.E.C. 21-100 high-resolution instrument. The results are quoted as *m/e* values for the lowest isotopic species except in the case of bromo-compounds, when values for ^{79}Br and ^{81}Br are given.

Dimethylformamide and triethylamine were stored over sodium hydroxide for at least 4 days prior to use.

Most of the microanalyses were carried out by Drs. F. and E. Pascher, Bonn.

Hydrazonyl Bromides.—Thiophen-2-carbaldehyde phenylhydrazone [from the aldehyde (11·2 g)], suspended in glacial acetic acid (250 ml), was treated with bromine (23 ml) in acetic acid (100 ml) with stirring and cooling for 1 h. The cooled mixture was stirred for a further 1·5 h and the product was then isolated in the normal way.[1] N-(2,4-*Dibromophenyl*)-N′-(α,5-*dibromo*-2-*thenylidene*)*hydrazine* (Ig) (33·7g, 65%) crystallized from ethanol–ethyl acetate as pale green needles, m.p. 147—148° (Found: C, 25·4; H, 1·3; Br, 61·9; N, 5·5; S, 6·3. $C_{11}H_6Br_4N_2S$ requires C, 25·5; H, 1·2; Br, 61·8; N, 5·4; S, 6·2%); δ (tetrahydrofuran; 100 MHz), 8·40 (s, NH), 7·67—7·22 (3H, m), and 7·23 (A) and 7·07 (B) p.p.m. (ABq, *J* 4·0 Hz).

Alternatively, the aldehyde was converted into the 5-bromo-derivative; [7] δ (neat) 9·87 (1H, s), and 7·68 (A) and 7·26 (B) p.p.m. (ABq, *J* 4·0 Hz). The derived phenylhydrazone (14·05 g), m.p. 110—112° (lit.,[7] 111—112°), bromine (9 ml), and acetic acid (250 ml) gave, as in the previous experiment, compound (Ig) (15·1 g, 58%) as pale green needles, m.p. and mixed m.p. 147—148° (from ethanol–ethyl acetate).

p-Chlorobenzaldehyde (26 g) was similarly converted into N-(α-*bromo*-p-*chlorobenzylidene*)-N′-(2,4-*dibromophenyl*)-*hydrazine* (Ie) (53 g, 61%), which crystallized from ethanol–ethyl acetate (charcoal) as needles, m.p. 145—146° (Found: C, 33·7; H, 1·7; N, 6·2. $C_{13}H_8Br_3ClN_2$ requires C, 33·4; H, 1·7; N, 6·0%); δ (CCl_4) 8·55 (NH, s), 7·78 (A) and 7·32 (B) (A_2B_2q, *J* 9 Hz), and 7·60—7·26 p.p.m. (3H, m).

p-Methoxybenzaldehyde (24 ml) similarly gave compound (If) (48 g, 55%) as needles, m.p. 132° (lit.,[8] 135°) [from ethyl acetate (charcoal)]; δ (CCl_4) 8·45 (NH, s), 7·75 (A) and 6·80 (B) (A_2B_2q, *J* 9 Hz), 7·60—7·24 (3H, m), and 3·80 p.p.m. (3H, s).

Reaction of Hydrazonyl Bromides with Sodium Acetate in Acetic Acid.—Essentially the procedure described for (Ic),[9] with *ca.* 5 equiv. of anhydrous sodium acetate in glacial acetic acid, was employed: (Ic) (9·0 g) gave the hydrazide (IIc) (7·25 g, 87%) as needles, m.p. 154—155° (lit.,[9] 158—159°) (from benzene).

Compound (Id) [1a] (3·72 g.) gave the hydrazide (IId) (3·2 g, 86%) as matted needles, m.p. 174—175° (from benzene) (Found: C, 51·45; H, 3·5; N, 8·0. Calc. for $C_{15}H_{12}BrFN_2O_2$: C, 51·3; H, 3·4; N, 8·0%); a sample, m.p. 175·5—176°, of (IId) had been prepared previously (P. D. Callaghan; *cf.* ref. 1*b*) by use of sodium acetate in acetonitrile.

N-*Acetyl*-N′-p-*chlorobenzoyl*-N-(2,4-*dibromophenyl*)*hydrazine* (IIe) (3·7 g, 86%), from (Ie) (4·67 g), crystallized from hexane–toluene as needles, m.p. 169·5—170·5° (Found: C, 40·35; H, 2·5; N, 6·35. $C_{15}H_{11}Br_2ClN_2O_2$ requires C, 40·35; H, 2·45; N, 6·3%); $\nu_{max.}$ (KBr) 1670br cm^{-1} (C=O).

N-*Acetyl*-N′-(2,4-*dibromophenyl*)-N′-p-*methoxybenzoylhydrazine* (IIf) (3·9 g, 88%), from (If) (4·64 g), crystallized from hexane–toluene as needles, m.p. 153—154° (Found: C, 43·6; H, 3·1; N, 6·5. $C_{16}H_{14}Br_2N_2O_3$ requires C, 43·45; H, 3·15; N, 6·35%); $\nu_{max.}$ 1670br cm^{-1}.

N-*Acetyl*-N′-(5-*bromo*-2-*thenoyl*)-N-(2,4-*dibromophenyl*)-*hydrazine* (IIg) (4·1 g, *ca.* 84%), from (Ig) (5·18 g), crystallized from toluene as fawn plates, m.p. 104·5—105° (Found: C, 38·5; H, 2·75; N, 4·8. $C_{13}H_9Br_3N_2O_2S$ requires 31·4; H, 1·2; N, 5·65. $C_{13}H_9Br_3N_2O_2S,C_7H_8$ requires C, 40·75; H, 2·9; N, 4·75%); $\nu_{max.}$ 1670br cm^{-1}; *m/e* 500/498/496/494 (M^+), 458/456/454/452 ($M^+ - CH_2{\cdot}CO$), 295/293/291 ($Br_2C_6H_3NHAc$), 267/265/263, 253/251/249 ($Br_2C_6H_3NH_2$), 235/233/231, 226/224/222, 207/205 ($BrC_4H_2S{\cdot}CO{\cdot}NH_2$), 191/189, 170/168, 163/161, 156/154, 119, 117, 111, 92 (M^+, toluene), 91, 82, 65, 63, 56, and 43.

Under these conditions, compound (Ia) (2·13 g; sample from I. T. Barnish; *cf.* ref. 1*a*) gave N-*benzoyl*-N′-(2-*bromo*-4-*ethoxycarbonylphenyl*)*hydrazine* (IIIa) (1·0 g, 59%) as needles, m.p. 134° (from hexane–toluene) (Found: C, 53·15; H, 4·05; N, 7·55. $C_{16}H_{15}BrN_2O_3$ requires C, 52·9; H, 4·15; N, 7·7%); $\nu_{max.}$ 1700 and 1650 cm^{-1}. Attempts to acetylate compound (IIIa) with acetic an-

[5] J. B. Aylward and F. L. Scott, *J. Chem. Soc.* (*C*), 1970, 968.
[6] R. Huisgen and R. Fleischmann, *Annalen*, 1959, **623**, 47.
[7] S. Gronowitz, *Arkiv Kemi*, 1955, **8**, 87.
[8] R. Ciusa and M. Mega, *Gazzetta*, 1928, **58**, 836.
[9] F. D. Chattaway and A. J. Walker, *J. Chem. Soc.*, 1925, **127**, 975.

hydride in acetic acid or in triethylamine were unsuccessful.

Reaction of Compound (Ib) [10] *with Sodium Acetate in Dimethylformamide.*—A solution of *N*-α-bromobenzylidene-*N'*-(2-bromo-4-nitrophenyl)hydrazine (Ib) (3·99 g, 0·01 mol) and anhydrous sodium acetate (9 g, *ca.* 10 equiv.) in dry dimethylformamide (30 ml) was boiled under reflux for 20 min, then cooled and poured into water (750 ml) containing acetic acid (20 ml). The precipitate was filtered off, dried, and crystallized from ethanol–ethyl acetate to give *4-acetyl-7-nitro-2-phenyl-4H-1,3,4-benzoxadiazine* (Vb) (2·2 g, 74%) as yellow needles, m.p. 204—205° (Found: C, 60·85; H, 4·05. $C_{15}H_{11}N_3O_4$ requires C, 60·6; H, 3·7%); $\nu_{max.}$ 1690 cm^{-1} (C=O). An attempt to deacetylate (Vb) with methanolic sodium methoxide (1 h reflux) gave a yellow gum containing at least four components (t.l.c.).

The foregoing reaction was repeated, except that the solution was heated to reflux and then poured immediately into 10% acetic acid (750 ml). The crude product, which contained (Vb) (t.l.c., i.r. spectrum), crystallized from ethanol–ethyl acetate to give *N*-(2-bromo-4-nitrophenyl)-*N'*-(α-ethoxybenzylidene)hydrazine (2·7 g, 74%) as yellow needles, m.p. 142·5—143·5° (lit.,[5] 149°) (Found: C, 49·25; H, 3·9; Br, 22·15. Calc. for $C_{15}H_{14}BrN_3O_3$: C, 49·45; H, 3·85; Br, 22·0%); δ ($CDCl_3$) 9·15 (NH, s), 8·58—7·50 (8H, m), 4·29 (2H, q), and 1·59 p.p.m. (3H, t).

7-Bromo-2-phenyl-4H-1,3,4-benzoxadiazine (VIc) [*from the Hydrazide* (IIc)].—A mixture of *N*-acetyl-*N'*-benzoyl-*N*-(2,4-dibromophenyl)hydrazine (IIc) (4·12 g, 0·01 mol), dimethylformamide (25 ml), triethylamine (5 ml), and sodium hydroxide (0·4 g, 0·01 mol) was boiled under reflux for 2·5 h. The mixture was cooled and poured into 5% acetic acid (450 ml). The green solid was filtered off, washed with water, dried, and chromatographed on Florisil (benzene as eluant). The fraction containing the yellow fluorescent product was collected and evaporated. Crystallization of the resulting solid from benzene–hexane gave *7-bromo-2-phenyl-4H-1,3,4-benzoxadiazine* (VIc) (1·3 g, 39%) as yellow needles, m.p. 151—152° (Found: C, 53·9; H, 3·0; Br, 27·75. $C_{13}H_9BrN_2O$ requires C, 54·0; H, 3·1; Br, 27·7%); δ [$(CD_3)_2SO$; 100 MHz] 8·86 (NH, s), 7·84—7·70 (2H, m), 7·52—7·34 (3H, m), 7·13—7·00 (2H, m), and 6·51 p.p.m. (1H, d, *J* 8·8 Hz).

Conditions for an optimum yield of (VIc) were not investigated; other materials present in the crude product included (IIc), (IIIc), and two unidentified minor products (t.l.c.). A separate experiment showed that compound (IIIc) did not react to give (VIc) under the foregoing conditions. Further, compound (IIc) did not react if sodium hydroxide was omitted.

4-Acetyl-7-bromo-2-phenyl-4H-1,3,4-benzoxadiazine (Vc) [*from Compound* (VIc)] *and Hydrolysis thereof.*—A solution of compound (VIc) (0·4 g) in acetic anhydride (10 ml) and acetic acid (10 ml) was boiled under reflux for 15 min, then cooled, and poured into water (250 ml). The precipitated solid was filtered off and dried. Crystallization from hexane gave the *4-acetyl derivative* (Vc) (0·3 g, 63%) as needles, m.p. 138° (Found: C, 54·3; H, 3·35; N, 8·55. $C_{15}H_{11}BrN_2O_2$ requires C, 54·4; H, 3·3; N, 8·45%); $\nu_{max.}$ 1680 cm^{-1} (C=O); δ [$(CD_3)_2SO$; 100 MHz] 8·09 (1H, d, *J* 8·8 Hz), 7·98—7·85 (2H, m), 7·65—7·48 (3H, m), 7·40—7·22 (2H, m), and 2·42 p.p.m. (3H, s).

A mixture of the *N*-acetyloxadiazine (Vc) (1·1 g), sodium hydroxide (0·2 g), dimethylformamide (15 ml), and triethylamine (5 ml) was boiled under reflux for 1 h, cooled, and poured into water (400 ml) containing acetic acid (20 ml). The precipitated solid was filtered off and dried. Crystallization from benzene–hexane gave the oxadiazine (VIc) (0·65 g, 68%) as yellow needles, m.p. and mixed m.p. 151—152°.

4-Acetyl-7-bromo-2-phenyl-4H-1,3,4-benzoxadiazine (Vc) [*from the Hydrazide* (IId)].—A mixture of the hydrazide (IId) (1·75 g), dimethylformamide (25 ml), and triethylamine (5 ml) was boiled under reflux for 2·5 h, then cooled, and poured into 5% acetic acid (700 ml). The solid was filtered off and dried to give the *N*-acetyloxadiazine (Vc) (1·50 g, 93%), which crystallized from hexane as needles, m.p. and mixed m.p. 138°.

7-Bromo-2-(p-chlorophenyl)-4H-1,3,4-benzoxadiazine (VIe) *and Acetylation thereof.*—A mixture of *N*-acetyl-*N'*-*p*-chlorobenzoyl-*N*-(2,4-dibromophenyl)hydrazine (IIe) (2·23 g), dimethylformamide (25 ml), triethylamine (5 ml), and sodium hydroxide (0·2 g) was boiled under reflux for 2·5 h, and the crude product, isolated as from the corresponding reaction of (IIc), was chromatographed on Florisil (toluene as eluant). The fraction containing the yellow fluorescent product was collected and evaporated, and the residue crystallized from hexane–toluene to give the *benzoxadiazine* (VIe) (0·5 g, 25%) as pale green prisms, m.p. 185—186° (Found: C, 48·5; H, 2·45; N, 8·6. $C_{13}H_8BrClN_2O$ requires C, 48·3; H, 2·5; N, 8·65%). The crude product also contained starting material (IIe) (t.l.c.).

The oxadiazine (VIe) (0·2 g) was acetylated as for (VIc) to give *4-acetyl-7-bromo-2-(p-chlorophenyl)-4H-1,3,4-benzoxadiazine* (Ve) (0·18 g, 75%), as needles, m.p. 180—181° (from hexane) (Found: C, 49·2; H, 2·7. $C_{15}H_{10}BrClN_2O_2$ requires C, 49·3; H, 2·75%); $\nu_{max.}$ 1680 cm^{-1}.

4-Acetyl-7-bromo-2-(p-methoxyphenyl)-4H-1,3,4-benzoxadiazine (Vf).—A mixture of *N*-acetyl-*N*-(2,4-dibromophenyl)-*N'*-*p*-methoxybenzoylhydrazine (IIf) (2·21 g), dimethylformamide (25 ml), triethylamine (5 ml), and sodium hydroxide (0·2 g) was boiled under reflux for 2·5 h, cooled, and poured into 5% acetic acid (800 ml). The white solid was filtered off, dried, and crystallized (twice) from ethanol–ethyl acetate to give the *benzoxadiazine* (Vf) (0·8 g, 45%) as spongy needles, m.p. 148—149° (Found: C, 53·05; H, 3·55; Br, 22·3. $C_{16}H_{13}BrN_2O_3$ requires C, 53·2; H, 3·6; Br, 22·15%); $\nu_{max.}$ 1680 cm^{-1}.

Attempted hydrolysis of (Vf) with ethanolic hydrochloric acid (4 h reflux) gave a dark intractable oil.

4-Acetyl-7-bromo-2-(5-bromo-2-thienyl)-4H-1,3,4-benzoxadiazine (Vg).—A mixture of *N*-acetyl-*N'*-(5-bromo-2-thenoyl)-*N*-(2,4-dibromophenyl)hydrazine (IIg) (2·0 g), dimethyl formamide (20 ml), triethylamine (5 ml), and sodium hydroxide (0·16 g) was boiled under reflux for 2·5 h. The crude product, isolated as for (Vf), contained starting material (IIg). The *benzoxadiazine* (Vg) (0·1 g, *ca.* 6%), separated by chromatography on Florisil (toluene as eluant), crystallized from benzene–hexane as cream needles, m.p. 184° (resolidifying, and not melting again below 260°) (Found: C, 37·35; H, 1·95; Br, 38·5. $C_{13}H_8Br_2N_2O_2S$ requires C, 37·5; H, 1·9; Br, 38·45%); $\nu_{max.}$ 1690 cm^{-1}.

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[10] J. M. Burgess and M. S. Gibson, *Tetrahedron*, 1962, **18**, 1001.