The Reactions of 2-Alkynylbenzaldehydes with Hydrazides: a Route to Isoquinoline *N*-Imines

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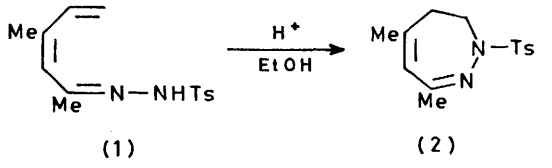
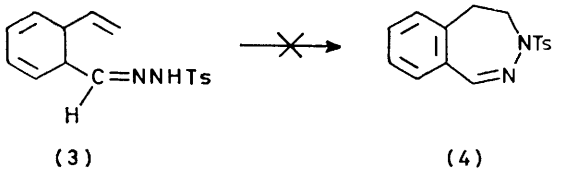
Sulphonyl- and acyl-hydrazones of 2-ethynylbenzaldehyde cyclise in the presence of base to give isoquinoline *N*-imines in moderate yield. The suggested mechanism involves primary formation of the hydrazone anion followed by nucleophilic attack on the alkyne bond, either by the anionic nitrogen to give an unstable 3*H*-2,3-benzodiazepine which rearranges to the isoquinoline *N*-imine, or by the neutral imine nitrogen to give the isoquinoline system directly. Attempts to extend the reaction to the semicarbazone and 2,4-dinitrophenylhydrazone were not successful.

We have recently shown that sulphonyl-[1] and acyl-hydrazones[2] of some αβ,γδ-unsaturated carbonyl compounds, *e.g.* (1), cyclise under acid conditions to give 2-



(1) (2)

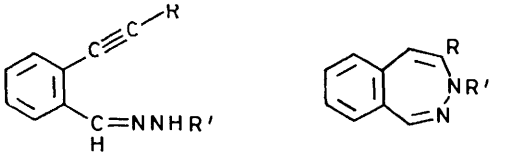


(3) (4)

substituted 3,4-dihydro-1,2-diazepines (2). The success of this reaction is strongly dependent on the nature and position of the substituents on the diene system and on the olefinic or aromatic nature of the unsaturation. For example, compounds such as (3) in which the αβ-double bond is part of a benzene ring do not cyclise to give (4). This paper describes an attempt to extend reactions of this type to compounds similar to (3) but having γδ-acetylenic unsaturation. Since alkynes are normally more susceptible than alkenes to nucleophilic attack it was hoped that (5) would cyclise under mild conditions to give the virtually unknown and apparently unstable[3] 3*H*-2,3-benzodiazepine system (6).

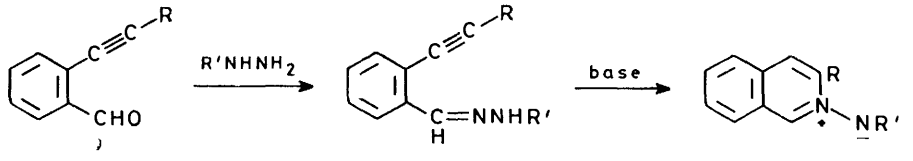
RESULTS AND DISCUSSION

2-Ethynylbenzaldehyde (7a) was readily converted to the tosylhydrazone (8a) by treatment with *p*-toluenesulphonylhydrazide under neutral or acid conditions.



(5) (6)

The tosylhydrazone cyclised readily in the presence of mild base at room temperature to give, not the benzodiazepine (6; R = R' = H), but isoquinoline *N*-*p*-toluenesulphonylimine (9a) in moderate yield (*ca.* 50%).



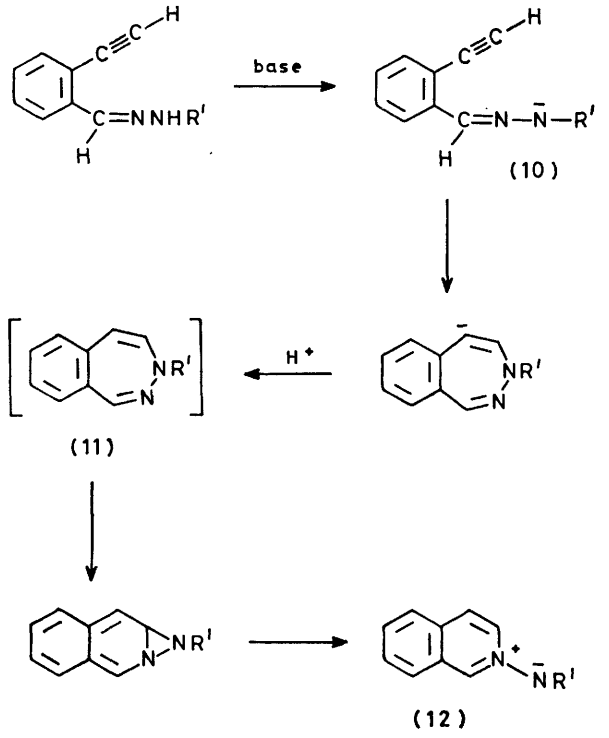
(7) (8) (9)

	R	R'	Yield (%) (8)	Yield (%) (9)
a;	H	Ts	98	48
b;	H	SO_2Me		40
c;	H	SO_2Ph		40
d;	H	COPh	61	77
e;	H	$CONH_2$	67	
f;	H	$2,4\text{-}(NO_2)_2C_6H_3$	77	
g;	Ph	Ts	77	
h;	Ph	COPh	80	

The bases used were sodium carbonate and 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU); cyclisation also occurred when an attempt was made to separate the *syn*- and *anti*-isomers of the tosylhydrazone on an alumina column. Similar cyclisations of the methanesulphonyl- and benzenesulphonyl-hydrazones gave the

analogous products (9b) and (9c) in 40% yields. No other pure products were isolated.

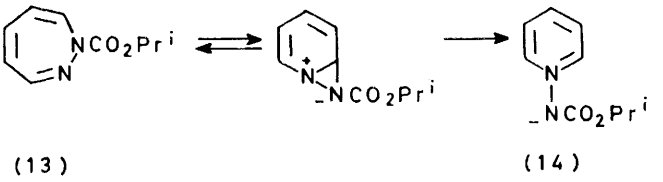
The benzoylhydrazone (8d) required more strongly basic conditions; it failed to cyclise with sodium carbonate but with DBU gave the *N*-benzoylimine (9d)



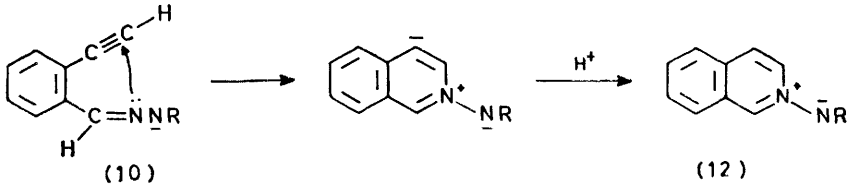
SCHEME 1

in 77% yield. The semicarbazone (8e) and the 2,4-dinitrophenylhydrazone (8f) were also prepared but could not be cyclised with sodium carbonate, DBU, sodium ethoxide, or cuprous chloride. No reaction occurred with the first two bases and with the last two the hydrazones were consumed but gave only polymeric material. An attempt to extend this reaction to the synthesis of 3-phenylisoquinoline *N*-imines (9g and h) was not successful. The tosylhydrazone (8g) reacted slowly at room temperature in the presence of sodium carbonate and DBU but gave only polymeric material: the absence of the *N*-tosylimine (9g) was shown by t.l.c. monitoring, using for comparison a sample of (9g) prepared by another route.[4] A control experiment showed that (9g) was stable under the reaction conditions. The analogous benzoylhydrazone (8h) did not react in the presence of either sodium carbonate or DBU.

The experimental data point clearly to the participation of the hydrazone anions (10) in the cyclisation process, since the strength of base required to induce cyclisation is related to the nature of R'. The sulphonylhydrazones (8a—c) would be expected to have the most acidic NH protons and these were readily cyclised by the weak bases sodium carbonate and alumina. The lower acidity of the NH proton in the benzoylhydrazone (8d) required the stronger base DBU to promote cyclisation, while (8e and f), which have weaker electron-withdrawing groups on nitrogen, could not be cyclised by DBU. The use of the more nucleophilic alkoxide bases induced polymerisation possibly *via* attack on the alkyne. The subsequent cyclisation pathway can be rationalised in two ways. In Scheme 1 the hydrazone anion cyclises *via endo*-attack of the anionic nitrogen on the alkyne bond to give 3*H*-2,3-benzodiazepine (11) which rapidly rearranges to give the isolated product. The aromatic isoquinoline N-imine would be expected to be more stable than the potentially anti-aromatic benzodiazepine (11) but it should be noted that this mechanism requires the conversion of (11) into (12) to be much more rapid than has been observed for the analogous monocyclic compounds (13) to (14). The diazepine (13) can be converted into (14), but requires the more forcing conditions of hot acetic acid.[5] However there is support for the suggested instability of (11) from the work of Garkusha-Bozhko *et al.*,[3] who report their involvement



as intermediates in the synthesis of isoquinoline *N*-imines *via* the reaction of isoquinolinium salts with hydrazones. In the alternative route shown in Scheme 2 the hydrazone anion cyclises by nucleophilic attack of the neutral nitrogen thus forming the six-membered ring directly. Even though the imine nitrogen is not nucleophilic enough in the hydrazone itself to induce cyclisation, its nucleophilicity would be expected to be much enhanced by the adjacent negative charge in the anion. The data do not allow differentiation between these two reaction paths.



SCHEME 2

EXPERIMENTAL

2-Ethynylbenzaldehyde, m.p. 60 °C (lit.,[6] 60—60.5 °C), was prepared by Ojima's method.[6]

2-*Phenylethynylbenzaldehyde*.—n-Butyl-lithium (9.95 ml of a 1.58M solution in hexane, 15.7 mmol) was added slowly to a stirred solution of 2-bromodiphenylacetylene [7] (2.00 g, 7.8 mmol) in dry ether (5 ml) kept at −30 °C under nitrogen. After the addition the mixture was stirred at −30 °C for 45 min and then at 0 °C for 1 h. Dry dimethylformamide (1.2 ml) was then added slowly and the mixture was allowed to warm up to room temperature and was stirred overnight. Saturated ammonium chloride solution (25 ml) was added and the mixture was extracted with benzene (3 × 50 ml). After washing with water (2 × 25 ml) the benzene extract was dried over magnesium sulphate and evaporated under reduced pressure to give an orange oil (2.0 g) which was distilled to give 2-phenylethynylbenzaldehyde (1.20 g, 75%), b.p. 150 °C at 0.1 mmHg (Found: C, 87.2; H, 5.2. $C_{15}H_{10}O$ requires C, 87.35; H, 4.9%); δ($CDCl_3$) 10.64 (s, 1 H) and 7.1—8.0 (m, 9 H, aromatic); $\nu_{max.}$ (film) 1 690 cm^{-1} (C=O).

Reactions of 2-Ethynylbenzaldehyde with Hydrazides.—All reactions were carried out under nitrogen in the dark. (i) p-*Toluenesulphonylhydrazide*. (*a*) 2-Ethynylbenzaldehyde (0.600 g, 4.61 mmol), *p*-toluenesulphonylhydrazide (0.900 g, 4.83 mmol), and concentrated hydrochloric acid (2 drops) in ethanol (15 ml) were stirred for 1 h at room temperature, when t.l.c. [alumina, light petroleum–ether (95 : 5)] showed complete consumption of the aldehyde and the formation of a single product. The solvent was removed on a rotary evaporator to leave crude 2-ethynylbenzaldehyde tosylhydrazone (1.373 g, 98%) as a yellow oil which could not be crystallised * (Found: M^+, 298.075 473. $C_{16}H_{14}N_2O_2S$ requires *M*, 298.077 544); δ($CDCl_3$) 2.41 (s, Me), 3.01 (s, ≡CH), 7.1—8.0 (m, 8 H, aromatic), 8.07 (s, NH), and 8.25 (s, HC=N). A solution of the tosylhydrazone (1.373 g) in ethanol (15 ml) was mixed with a solution of sodium carbonate (4 g, 0.04 mol) in water (2 ml) and the mixture was stirred at room temperature for 18 h. Water (50 ml) was added and the mixture was extracted with methylene chloride (2 × 50 ml). The organic layer was dried and evaporated to give a yellow powder (1.20 g) which was crystallised from ethanol to give isoquinoline *N*-*p*-toluenesulphonylimine (0.642 g, 47%), m.p. 226—227 °C (lit.,[8] 228—229 °C), with ^1H n.m.r. and i.r. spectra identical to those reported.[8] Evaporation of the mother-liquor gave a dark oil (0.558 g) from which no pure product could be obtained by chromatography.

(*b*) A similar experiment in which 2-ethynylbenzaldehyde (0.200 g, 1.54 mmol), *p*-toluenesulphonylhydrazide (0.300 g, 1.61 mmol), and concentrated hydrochloric acid (2 drops) in ethanol (10 ml) were stirred at room temperature for 1 h and then for a further 24 h after the addition of a solution of sodium carbonate (0.5 g, 4.7 mmol) in water (1 ml) gave isoquinoline *N*-*p*-toluenesulphonylimine in 48% yield.

(*c*) 2-Ethynylbenzaldehyde (0.100 g, 0.77 mmol), *p*-toluenesulphonylhydrazide (0.150 g, 0.80 mmol), and concentrated hydrochloric acid (1 drop) in ethanol (10 ml) were stirred at room temperature for 1 h; the acid was neutralised with solid sodium hydrogen carbonate, 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) (0.060 g, 0.4 mmol) was added and the mixture stirred at room temperature for 2 days. The usual work-up gave isoquinoline *N*-toluenesulphonylimine in 35% yield.

(ii) *Benzenesulphonylhydrazide*. A reaction similar to (i) (b) above gave isoquinoline *N*-benzenesulphonylimine (40%), m.p. 258—260 °C (decomp.) (butanol) (Found: C, 63.2; H, 4.35; N, 9.6. $C_{15}H_{12}N_2O_2S$ requires C, 63.4; H, 4.25; N, 9.85%); δ[$(CD_3)_2SO$] 7.1—8.5 (m, 11 H, aromatic) and 9.53 (s, H-1); $\nu_{max.}$ (Nujol) 1 605 (C=N), and 1 285 and 1 130 cm^{-1} (SO_2).

(iii) *Methanesulphonylhydrazide*. A reaction similar to (i) (b) above gave isoquinoline *N*-methanesulphonylimine (40%), m.p. 220 °C (propanol) (Found: C, 53.9; H, 4.5; N, 12.5. $C_{10}H_{10}N_2O_2S$ requires C, 54.0; H, 4.5; N, 12.6%); δ[$(CD_3)_2SO$] 2.70 (s, Me), 7.8—8.6 (m, 6 H, aromatic), and 9.70 (d, *J* 1 Hz, H-1); $\nu_{max.}$ (Nujol) 1 605 (C=N), and 1 275 and 1 120 cm^{-1} (SO_2).

(iv) *Benzoylhydrazide*. 2-Ethynylbenzaldehyde (0.204 g, 1.57 mmol), benzoylhydrazide (0.214 g, 1.57 mmol), and concentrated hydrochloric acid (3 drops) in ethanol (10 ml) were stirred at room temperature. The white precipitate which formed after *ca.* 5 min was filtered off (0.368 g) and recrystallised from ethanol to give 2-ethynylbenzaldehyde benzoylhydrazone (0.236 g, 61%), m.p. 162—164 °C (Found: C, 77.2; H, 4.75; N, 11.2. $C_{16}H_{12}N_2O$ requires C, 77.4; H, 4.9; N, 11.3%); δ[$(CD_3)_2SO$] 4.30 (s, ≡CH), 7.2—8.2 (m, 10 H, aromatic and NH), and 8.91 (s, HC=N); $\nu_{max.}$ (Nujol) 3 230 (N–H), 1 650 (C=O), and 1 610 cm^{-1} (C=N). The benzoylhydrazone (0.100 g, 0.403 mmol) and DBU (80 mg, 0.6 mmol) were stirred as a slurry in ethanol (5 ml) at room temperature for 3 days. The solid was filtered off to give isoquinoline *N*-benzoylimine (0.040 g), and the filtrate was evaporated to give a dark solid which was crystallised from ethanol to give a further crop of the *N*-benzoylimine (0.037 g, total yield 77%), m.p. 187—188 °C (lit.,[8] 188 °C), i.r. and ^1H n.m.r. spectra identical with those reported.[8]

(v) *Semicarbazide hydrochloride*. 2-Ethynylbenzaldehyde (0.154 g, 1.18 mmol), semicarbazide hydrochloride (0.132 g, 1.18 mmol), and concentrated hydrochloric acid (2 drops) in ethanol (5 ml) were stirred at room temperature for 2 h. The white precipitate (0.182 g) was crystallised from ethanol to give 2-ethynylbenzaldehyde semicarbazone (0.149 g, 67%), m.p. 188.5—190 °C (Found: C, 64.3; H, 4.9; N, 22.4. $C_{10}H_9N_3O$ requires C, 64.2; H, 4.85; N, 22.5%); δ[$(CD_3)_2SO$] 4.22 (s, CH), 6.40 (s, NH_2), 7.1—8.2 (m, 5 H, aromatic and NH), and 8.32 (s, HC=N); $\nu_{max.}$ (Nujol), 3 470, 3 260, 3 140 (NH and NH_2), and 1 700 cm^{-1} (C=O). Attempts to cyclise the semicarbazone to isoquinoline *N*-amidoimine with sodium carbonate, DBU, cuprous chloride, and sodium ethoxide were unsuccessful. In the first two cases no reaction took place and in the last two only polymeric material was obtained.

(vi) 2,4-*Dinitrophenylhydrazine*. A similar reaction to (v) above gave 2-ethynylbenzaldehyde 2,4-dinitrophenylhydrazone (77%), m.p. 200—205 °C (Found: C, 57.8; H, 3.3; N, 17.9. $C_{15}H_{10}N_4O_4$ requires C, 58.1; H, 3.25; N, 18.1%); δ[$(CD_3)_2SO$] 4.65 (s, ≡CH), 7.3—8.9 (m, 8 H, aromatic and NH), and 9.01 (s, HC=N); $\nu_{max.}$ (Nujol) 3 260 (NH) and 1 610 cm^{-1} (C=N). Attempts to cyclise this hydrazone as in (v) above gave similar results.

Reactions of 2-Phenylethynylbenzaldehyde with Hydrazides.—(i) p-*Toluenesulphonylhydrazide*. Reaction under the usual conditions gave the *p*-toluenesulphonylhydrazone (77%), m.p. 158—161 °C (Found: C, 70.8; H, 4.9; N, 7.4. $C_{22}H_{18}N_2O_2S$ requires C, 70.6; H, 4.85; N, 7.5%);

* Attempted purification by chromatography on alumina gave only the cyclised product isoquinoline *N*-toluenesulphonylimine.

$\delta(CDCl_3)$ 2.25 (s, CH_3), 7.1—8.0 (m, 13 H, aromatic), 8.15 (s, NH), 8.30 (s, HC=N); $\nu_{max.}$ (Nujol) 3 220 (NH), 1 600 (C=N), and 1 320 and 1 165 cm^{-1} (SO_2).

Attempts to cyclise this hydrazone with sodium carbonate and DBU in ethanol at room temperature were not successful. After 3 days the hydrazone had been consumed but t.l.c. comparison with an authentic sample [4] showed the absence of 3-phenylisoquinoline *N*-tosylimine. Work-up and chromatography did not give any pure products.

(ii) *Benzoylhydrazide*. Reaction under the usual conditions gave 2-phenylethynylbenzaldehyde benzoylhydrazone (80%), m.p. 178—180 °C (Found: C, 81.2; H, 5.0; N, 8.6. $C_{22}H_{16}N_2O$ requires C, 81.5; H, 5.0; N, 8.6%); $\delta(CDCl_3)$ 7.1—8.0 (m, 14 H, aromatic), 8.70 (s, NH), and 9.45 (s, HC=N); $\nu_{max.}$ (Nujol) 3 180 (NH), 1 645 (C=O), and 1 610 cm^{-1} (C=N).

The hydrazone remained unchanged in the presence of sodium carbonate and DBU at room temperature, and gave only polymeric products with sodium methoxide and cuprous chloride.

[9/1346 *Received*, 22*nd August*, 1979]

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