The Synthesis of Terminal Enynes by Grignard Additions to Pyridazine 1-Oxide

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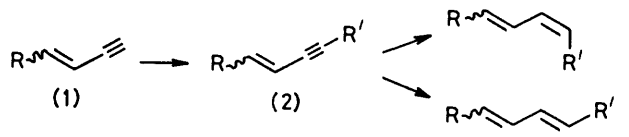
The ring opening of pyridazine 1-oxide by the Grignard reagents prepared from 3-bromochlorobenzene, bromobenzene, 1-bromonaphthalene, pent-1-yne, and 1-phenylbut-1-en-3-yne is shown to lead exclusively to the corresponding terminal *E*-enynes (3a), (3b), (5), (6), and (7) respectively. By contrast, alkyl Grignard reagents instead lead to the corresponding 1,3-dienes (9).

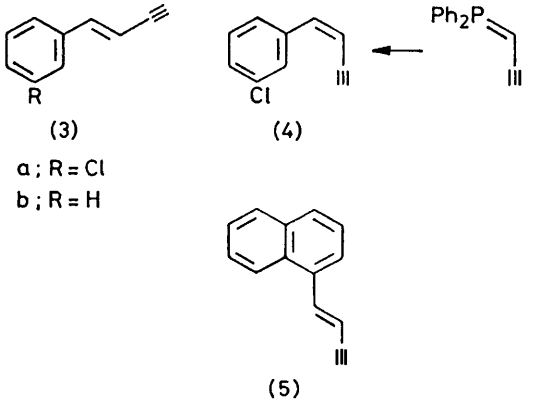
THE terminal enyne unit (1) is an important structural feature found in a number of biologically interesting natural products, *e.g.* histrionicotoxin from *Dendrobates histrionicus*,[1] and laurencin and related metabolites



(1) (2)

present in the seaweed *Laurencia*.[2] The corresponding ' internal ' enyne unit (2) is commonly found, along with polyacetylenes and allenes, in natural products from the Compositae and Umbelliferae.[3]

The partial reduction of internal *Z*- and *E*- enynes has long been recognised as an attractive route to the synthesis of conjugated dienes of predictable geometry.[4] In addition, these internal enynes are easily available *via* terminal enynes following metallation and reaction with electrophilic reagents.[5] The potential for terminal enynes in synthesis is thus considerable, and much effort has been expended, in recent years, towards developing routes to both *Z*- and *E*-enyne units.[6] An attractive route to terminal enynes, which permits the introduction of the entire four carbon enyne unit in one stage from a single precursor, is the ring opening of pyridazine 1-oxide by Grignard reagents (Scheme). This little investigated

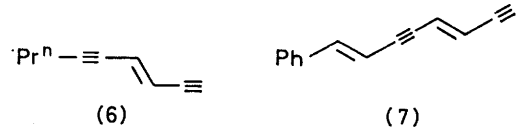


(3) (4) (5)

a ; R = Cl
b ; R = H

reaction has been examined briefly by Okusa *et al.*[7] and by Igeta *et al.*,[8] in the case of aryl Grignard reagents, who found that the reaction led to modest yields (30—40%) of 1-arylbut-1-en-3-ynes displaying predominantly *E*-stereochemistry. We were attracted by the possibility of use of this reaction as a general sequence for the preparation of a range of enyne precursors for subsequent elaboration to geometrically homogeneous polyene isobutylamide insecticides.

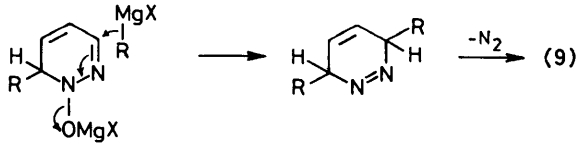
We first examined the reaction with aryl Grignard reagents in order to assess the stereospecificity of the overall sequence. Addition of pyridazine 1-oxide to the Grignard reagent from 3-bromochlorobenzene, followed by the usual work-up and chromatography, led exclusively to the *E*-enyne (3a) in 60% yield. The *E*-stereochemistry followed from the magnitude of the vicinal coupling (*J* 15 Hz) between the olefinic hydrogens in the ^{1}H n.m.r. spectrum of the enyne and by direct comparison with the corresponding *Z*-isomer (4) prepared from a Wittig condensation between 3-chlorobenzaldehyde and the phosphonium salt of propargyl bromide.[6c] In a similar manner the Grignard reagents prepared from bromobenzene and 1-bromonaphthalene led to the corresponding *E*-enynes (3b) and (5), respectively, in 52—77% yields.



(6) (7)

Reactions between pyridazine 1-oxide and the Grignard reagents from pent-1-yne and 1-phenylbut-1-en-3-yne (3b) also proceeded smoothly and gave the *E*-enediyne (6) and the *EE*-dienediyne (7), respectively. Attempts at reaction of the *N*-oxide with the more nucleophilic alkyl Grignard reagents, however, were less successful, and these reactions instead led to the corresponding 1,3-dienes [*viz.* (9)] by way of substitution rather than elimination from the intermediate (8) (Scheme).†

† An alternative mechanism for the formation of (9) is:



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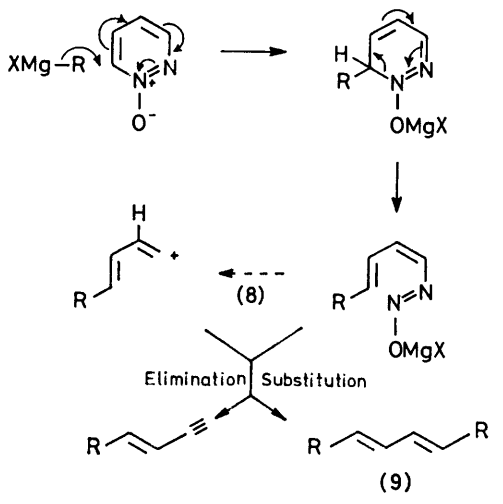

SCHEME

EXPERIMENTAL

As far as possible, all manipulations involving enynes were carried out in an inert atmosphere, and solvents were evaporated *in vacuo* at room temperature.

Reaction between Pyridazine 1-Oxide and Grignard Reagents. General Procedure.—A solution of pyridazine 1-oxide [9] (0.036 mol) in tetrahydrofuran (15 ml) was added dropwise to a stirred solution of the Grignard reagent [from Mg (0.04 g atom) and organohalide (0.04 mol)] in tetrahydrofuran (25 ml) maintained at 5—15 °C. The mixture was stirred at 25 °C for 0.5 h, then diluted with 2N-hydrochloric acid (*ca.* 50 ml) and extracted with ether (3 × 50 ml). The combined ether extracts were washed with sodium hydrogencarbonate solution and water, then dried and evaporated. Chromatography of the residue in n-hexane on silica gel gave the pure enyne.

(E)-1-(m-*Chlorophenyl*)*but*-1-*en*-3-*yne* (3a).—By the general procedure, the enyne was obtained (60%) as an oil, b.p. 70° at 1 mmHg, $\nu_{max.}$ (film) 3 300 and 2 100 cm^{-1}, τ 2.7—2.8 (4 H, m), 3.1 (d, *J* 15 Hz, ArC*H*:), 4.0 (dd, *J* 15 and 2 Hz, HC:C·C*H*:CH), and 7.0 (d, *J* 2 Hz, :C*H*). The corresponding *Z*-enyne (4), prepared from Wittig condensation between *m*-chlorobenzaldehyde (7 g) and propargyltriphenylphosphonium bromide [6c] (22.5 g) in acetonitrile (150 ml) and anhydrous ammonia (80 ml) at −50 °C, then purified by chromatography in benzene on silica gel, showed τ 2.0—2.5 (2 H, m), 2.7—2.9 (2 H, m), 3.45 (d, *J* 11 Hz, ArC*H*:), 4.3 (dd, *J* 11 and 2 Hz, HC:C·C*H*:CH), and 6.7 (d, *J* 2 Hz, :C*H*).

(E)-1-*Phenylbut*-1-*en*-3-*yne* (3b).—By the general procedure the enyne was obtained (76%) as an oil, b.p. 66—68° at 25 mmHg (lit.,[7] 49—50° at 2 mmHg), $\nu_{max.}$ (film) 3 300 and 2 095 cm^{-1}, τ 2.65br (5 H), 2.85 (d, *J* 15 Hz, ArC*H*:), 3.99 (dd, *J* 15 and 2 Hz, HC:C·C*H*:CH), and 6.98 (d, *J* 2 Hz, :C*H*) (Found: *m/e*, 128.061 4. Calc. for $C_{10}H_8$: *M*, 128.062 6).

(E)-1-(α-*Naphthyl*)*but*-1-*en*-3-*yne* (5).—By the general procedure, the enyne was obtained (52%) as an *oil*, $\nu_{max.}$ 3 281, 2 097, and 975 cm^{-1}, τ 2.7—3.0 (8 H, m), 3.85 (dd, *J* 16 and 2 Hz, HC:C*H*:CH), 6.9 (d, *J* 2 Hz, :CH) (Found: *m/e*, 178.077 8. $C_{14}H_{10}$ requires *M*, 178.078 2). The enyne was characterised by conversion into the corresponding Mannich base, with formaldehyde and dimethylamine, followed by quaternisation with methyl iodide; the NNN-*trimethyl*-5-(1-*naphthyl*)-(E)-*pent*-4-*en*-2-*ynylammonium iodide* crystallised from ethanol, m.p. 226° (Found: C, 57.4; H, 5.3; N, 3.7. $C_{18}H_{20}NI$ requires C, 57.3; H, 5.3; N, 3.7%).

(E)-*Non*-3-*ene*-1,5-*diyne* (6).—Pent-1-ynylmagnesium bromide was prepared in the usual manner from pent-1-yne and ethylmagnesium bromide. By the general procedure, the Grignard reagent and pyridazine 1-oxide gave the enyne (41%) as an *oil*, b.p. 56° at 4 mmHg, $\lambda_{max.}$(EtOH) 257 (ε 23 500), 260 (22 500), and 271 nm (21 600), $\nu_{max.}$ 3 350, 2 250, and 950 cm^{-1}, τ 4.07 (dt, *J* 16 and 1 Hz, CH_2·C:C·C*H*), 4.32 (dd, *J* 16 and 2 Hz, HC:C·C*H*:CH), 7.0 (d, *J* 2, :C*H*), 7.75 (dt, *J* 1 and 7 Hz, CH_2CH_2C:C·), 8.5 (tq, *J ca.* 7 Hz, $CH_3CH_2CH_2$), and 9.05 (t, *J* 7 Hz, CH_2CH_3), δ_C 123.7 (d), 118.5 (d), 96.5, 82.1, 81.1 (d), 79.0, 22.2 (t), 21.7 (t), and 13.5 (q) p.p.m. (Found: *m/e* 118.078 9. C_9H_{10} requires *M*, 118.072 5).

(EE)-1-*Phenylocta*-1,5-*diene*-3,7-*diyne* (7).—(*E*)-1-Phenylbut-1-en-3-ynylmagnesium bromide was prepared in the usual manner from (*E*)-1-phenylbut-1-en-3-yne and ethylmagnesium bromide. By the general procedure, the Grignard reagent and pyridazine 1-oxide gave the dienediyne (21%) as an unstable *oil*, $\lambda_{max.}$ 310 (infl.), 332, and 343 nm, $\nu_{max.}$ (film) 3 290, 2 180, 2 080, and 956 cm^{-1}, τ 2.5—2.8 (5 H, m), 3.0 (d, *J* 15 Hz, ArC*H*:), 3.7 (overlapping d, *J ca.* 15 Hz, :C*H*·C:C·C*H*), 4.0 (dd, *J* 15 and 2 Hz, HC:C·C*H*:CH·), and 6.85 (d, *J* 2 Hz, :C*H*) (Found: *m/e* 178.077 9. $C_{14}H_{10}$ requires *M*, 178.078 2).

Deca-4,6-*diene* (9; R = Pr^n).—By the general procedure, reaction between n-propylmagnesium bromide and pyridazine 1-oxide led to the *diene* (20%), $\lambda_{max.}$(EtOH) 231 nm (ε 19 680), τ 3.7—5.0 (4 H, m), 8.0 (dt, *J ca.* 7 Hz, CH_2-CH_2CH:), 8.7 (tq, *J ca.* 7 Hz, $CH_2CH_2CH_3$), and 9.1 (t, *J* 7 Hz, CH_2CH_3), δ_C 134.3 (d), 132.0 (d), 130.6 (d), 129.8 (d), 128.9 (d), 126.0 (d), 35.0 (t), 34.7 (t), 29.8 (t), 23.0 (t), 22.6 (t), and 13.6 (q) p.p.m. (Found: *m/e* 138.138 4. $C_{18}H_{18}$ requires *M*, 138.140 8) as a mixture of geometrical isomers.

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