The Synthesis of Furans from Acetylenic Epoxides and Diols

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Acetylenic αβ-epoxides react with dilute sulphuric acid and mercuric sulphate on heating to give furans in good yields; the reaction involves an internal hydration at a terminal acetylenic carbon atom. Under the influence of sulphuric acid alone, only small quantities of furans are formed; the major products are acetylenic diols. These have been shown to be probable intermediates in the formation of the furans. When the epoxides are treated with dilute sulphuric acid in the presence of ethanol, monoethers of acetylenic diols are formed. Acetylenic βγ-epoxides have also been shown to give furans in the mercuric sulphate-catalysed reaction with sulphuric acid.

SUBSTITUTED furans have been synthesised from several types of acetylenic intermediate since Heilbron *et al.*[1] prepared 2,5-dimethylfuran and 2-methylfuran from hex-3-en-5-yn-2-ol and pent-2-en-4-yn-1-ol respectively, under the influence of dilute sulphuric acid and mercuric sulphate. Acetylenic 1,2-diols have been isomerised by heating with mercuric chloride in ethanol [2] or by treatment with base followed by acid,[3] and prop-2-ynyl-substituted 1,3-diketones gave 3-acylfurans when heated with zinc carbonate.[4] The action of organic acids on acetylenic alkoxy-β-keto-esters has also given furans.[5] In addition, furan derivatives have been formed during the reaction between alkali metal acetylides and 1-chloro-2,3-epoxypropane,[6] and 5-methylfuran-2-acetic acid

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[1] I. M. Heilbron, E. R. H. Jones, P. Smith, and B. C. L. Weedon, *J. Chem. Soc.*, 1946, 54; I. M. Heilbron, E. R. H. Jones, and F. Sondheimer, *ibid.*, 1947, 1586.

[2] E. D. Venus-Danilova and V. M. Albitskaya, *J. Gen. Chem.* (*U.S.S.R.*), 1952, **22**, 879, 1611; L. A. Pavlova, *ibid.*, 1955, **25**, 1471; A. Fabrycy and Z. Wichert, *Roczniki Chem.*, 1968, **42**, 35, and references therein.

[3] S. Holand and R. Epsztein, *Compt. rend.*, 1965, **261**, 4449.

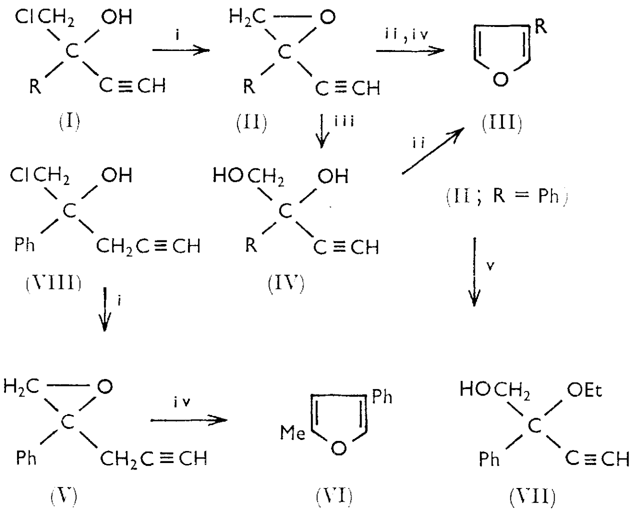
[4] K. E. Schulte, J. Reisch, and A. Mock, *Arch. Pharm.*, 1962, **295**, 627.

[5] Zh. A. Krasnaya, S. S. Yufit, T. S. Levchenko, and V. F. Kucherov, *Tetrahedron*, 1967, **23**, 3687.

[6] S. R. Landor and E. S. Pepper, *J. Chem. Soc.* (*C*), 1966, 2283; T. L. Jacobs, D. Dankner, and A. R. Dankner, *J. Amer. Chem. Soc.*, 1958, **80**, 864.

was one of the products of carboxylation of hex-3-en-5-yn-2-ol.[7]

We now describe the formation of furans from acetylenic epoxides (II) and (V), obtained from the readily available chloroacetylenic carbinols (I)[8] and (VIII). The method provides a simple synthesis of 3-substituted furans, a not very accessible class of compounds of interest in the field of natural products.[9]



Reagents: i, NaOH–ether; ii, aq.H_2SO_4–$HgSO_4$; iii, aq.H_2SO_4; iv, aq.EtOH–H_2SO_4–$HgSO_4$; v, aq.EtOH–H_2SO_4.

When the acetylenic αβ-epoxide,3,4-epoxy-3-methylbut-1-yne (II; R = Me), was distilled with 2N-sulphuric acid containing a catalytic amount of mercuric sulphate, *i.e.* subjected to the usual conditions for triple bond hydration, an oil (68%) was formed, the i.r. spectrum of which showed the absence of hydroxy and carbonyl absorptions. Distinctive bands indicated the presence of a furan nucleus (Table 1),[10] and the physical constants and n.m.r. spectrum (Table 2) confirmed that the oil was 3-methylfuran (III; R = Me).[11] If the same distillation was carried out in the absence of mercuric sulphate, no furan was formed, but if mercuric sulphate was then added to the reaction mixture and the distillation continued, 3-methylfuran was formed as before.

TABLE 1

I.r. spectra of furans

	$\nu_{max.}$ (cm.$^{-1}$) associated with the furan ring[10]					
3-Methylfuran[a]	3100w	1570w	1500m	1160s	1062m	875s
3-t-Butylfuran[a]	3120w	1570w	1505w	1164s	1064m	875s
3-Phenylfuran[b]	3100w	1570w		1160s	1055m	870s
5-Methyl-3-phenylfuran[b]	3100w	1550w		1128s	1074m	811 or 920s

[a] Liquid film. [b] Nujol mull.

TABLE 2

N.m.r. spectra of furans (CCl_4 solutions)

	Chemical shift (τ)				
	H-2	H-4	H-5	3-Substituent	5-Substituent
3-Methylfuran ...	2·92	3·89	2·80	8·03(s)	
3-t-Butylfuran ...	2·90	3·78	2·80	8·78(s)	
3-Phenylfuran * ...	2·35	3·40	2·60	2·43—2·90	
5-Methyl-3-phenylfuran	2·52	3·83		2·50—2·93	7·74(s)

In all spectra, signals integrated for the expected numbers of protons and were multiplets unless otherwise indicated (s = singlet).

* From the spectrum of this molecule, the protons in the furan ring have $J_{4,5}$ 1·8, $J_{2,5}$ 1·5, and $J_{2,4}$ 0·9 c./sec.

Alternatively, the epoxide (II; R = Me) could be ring-opened in the cold with 2N-sulphuric acid to give 3-methylbut-1-yne-3,4-diol (IV; R = Me), which, on distillation with sulphuric acid and mercuric sulphate, gave 3-methylfuran in comparable yield to the single-step process. It follows that acetylenic diols are probably intermediates in this type of reaction.

In a similar manner 3-t-butylfuran (III; R = Bu^t) (43%)[12] and 3-phenylfuran (III; R = Ph) (76%)[13] were prepared by distilling or heating under reflux the appropriate epoxides with sulphuric acid and mercuric sulphate, but in the case of the 3-phenyl compound a co-solvent such as dimethylformamide or ethanol was required, otherwise only decomposition products resulted. Omission of the catalyst from the reaction mixtures gave mainly ring-opened products, although, with the t-butyl epoxide, the furan was formed to the extent of 11% presumably because cyclisation is favoured in the intermediate diol containing adjacent fully substituted carbon atoms. Once formed, the 3-t-butylfuran was shown to be stable under the conditions employed. In the case of the phenyl compound, cyclisation to 3-phenylfuran only occurred to the extent of 0·5% in the absence of catalyst.

The major product of the reaction between 3,4-epoxy-3-phenylbut-1-yne (II; R = Ph) and 2N-sulphuric acid–ethanol (1 : 1) was 3-ethoxy-3-phenylbut-1-yn-4-ol (VII), the structure of which followed from analytical and spectroscopic evidence. The i.r. spectrum showed the presence of hydroxy- (3230 cm.$^{-1}$) and acetylenic (2110 cm.$^{-1}$) functions, and the n.m.r. spectrum (CCl_4) indicated the structure clearly, and showed that it could not be the isomeric 4-ethoxy-compound since the hydroxy-proton gave rise to a triplet (*J* 7 c./sec.), owing to coupling with the adjacent methylene protons. The methylene protons of the ethoxy-group were non-equivalent, exhibiting an AB pattern (*J* 9 c./sec.), further coupled to the adjacent methyl protons.[14]

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[8] E. R. H. Jones, B.P. 836,280.

[9] M. A. Gianturco and P. Friedel, *Canad. J. Chem.*, 1966, **44**, 1083.

[10] A. R. Katritzky and A. P. Ambler, 'Physical Methods in Heterocyclic Chemistry,' ed. A. R. Katritzky, Academic Press, London, 1963, vol. II, p. 199.

[11] D. M. Burness, *J. Org. Chem.*, 1956, **21**, 102; H. Gilman and R. R. Burtner, *J. Amer. Chem. Soc.*, 1933, **55**, 2903.

[12] N. I. Shuikin, B. L. Lebedev, V. G. Nikol'skii, O. A. Korytina, A. V. Kessenikh, and E. P. Prokof'ev, *Izvest. Akad. Nauk S.S.S.R., Ser. khim.*, 1967, 1618 (*Chem. Abs.*, 1968, **68**, 95607u).

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In all preparations of furans from acetylenic compounds prior to this work,[1-7] addition to the triple bond has taken place at a non-terminal carbon atom; this is the usual mode of addition in the case of monosubstituted acetylenes.[15a] The above synthesis shows that, in favourable circumstances, nucleophilic attack of oxygen can be directed to the normally prohibited terminal carbon atom.

The synthesis has been extended to acetylenic βγ-epoxides. When 4,5-epoxy-4-phenylpent-1-yne (V) reacted with aqueous ethanolic sulphuric acid in the presence of mercuric sulphate, attack at the sub-terminal carbon atom occurred to give 5-methyl-3-phenylfuran (VI) (77%).[16]

The reaction appears capable of considerable extension, especially since the necessary acetylenic epoxides can be obtained by epoxidation of readily available enynes.[15b]

EXPERIMENTAL

M.p.s were determined with a Büchi apparatus. I.r. spectra were obtained with a Perkin-Elmer model 137 spectrophotometer. N.m.r. spectra were determined at 60 Mc./sec. with a Varian A60 instrument. G.l.c. was carried out on two types of column: (A) 10% W/W S.E.52 on Chromosorb W(80—100 mesh) and (B) 0·5% ethylene glycol adipate polyester on micro-glass beads (diameter 100 μ).

3-*Methylfuran*.—3,4-Epoxy-3-methylbut-1-yne (2·46 g., 0·03 mole)[17] was added to a stirred solution of mercuric sulphate (0·3 g.) in 2N-sulphuric acid (25 ml.). Instantaneous reaction occurred, as shown by a rise in temperature to 35—40°. The mixture was distilled and the organic distillate, immiscible with water, was separated and dried ($MgSO_4$) (1·66 g., 68%). Distillation afforded 3-methylfuran [1·19 g., 48%; 98% pure by g.l.c. on column (A)], b.p. 65—66·5°/760 mm., n_D^{21} 1·4299; mercurichloride, m.p. 138·5—139·5° (lit.,[11] b.p. 65·5°/760 mm., n_D^{25} 1·4315; mercurichloride, m.p. 142°).

When the above experiment was carried out in the absence of mercuric sulphate, distillation afforded no organic material immiscible with water. However, when the mixture was cooled and mercuric sulphate added, redistillation afforded 3-methylfuran (59%; 93% pure by g.l.c.).

3-t-*Butylfuran*.—3,4-Epoxy-3-t-butylbut-1-yne (4·02 g., 0·032 mole) was added rapidly to 2N-sulphuric acid (25 ml.) containing mercuric sulphate (0·3 g.), and the whole was stirred vigorously for 20 min. Distillation gave an oil [2·8 g., 70%; 76% pure by g.l.c. on column (B)] which, on redistillation, afforded 3-t-butylfuran (1·72 g., 43%; 90% pure by g.l.c.), b.p. 56—64°/60 mm.

When the epoxide (2·0 g.) and 2N-sulphuric acid (12 ml.) were heated under reflux for 2 hrs., an oil was formed which (g.l.c.) contained 3-t-butylfuran (11%) and five other products.

Stability of 3-*t-Butylfuran*.—The furan (0·28 g.) and 2N-sulphuric acid (5 ml.) were heated under reflux with stirring for 2 hr. during which time some darkening took place. The mixture was cooled and the oil which remained was separated and dried ($MgSO_4$). It was shown by comparison with authentic material to be 3-t-butylfuran (0·2 g., 72% recovery).

3-*Phenylfuran*.—3,4-Epoxy-3-phenylbut-1-yne (1·45 g. 0·01 mole) in ethanol (10 ml.) was added in one portion to 2N-sulphuric acid (10 ml.) containing mercuric sulphate (0·2 g.); the mixture became warm. It was heated under reflux and stirred for 20 min., during which time an oil formed, then cooled and diluted with water; the gummy solid remaining was extracted into light petroleum (b.p. 40—60°). The extract was washed with sodium hydrogen carbonate solution and water, dried ($MgSO_4$), and evaporated to leave yellow crystals (1·25 g., 86%), m.p. 50—54°, which, on sublimation at 60—80°/14 mm., gave colourless platelets of 3-phenylfuran (1·10 g., 76%), m.p. 57—57·5° (lit.,[10] m.p. 58·5—59°, sublimed at 65°/25 mm.). The compound was unstable and decomposed during several weeks.

A similar experiment with dimethylformamide (10 ml.) as co-solvent instead of ethanol gave 3-phenylfuran (63%), m.p. 55—56·5° after sublimation.

5-*Methyl*-3-*phenylfuran*.— 4,5-Epoxy-4-phenylpent-1-yne (1·58 g., 0·01 mole) in ethanol (10 ml.) was added in one portion to a stirred solution of mercuric sulphate (0·2 g.) in 2N-sulphuric acid (10 ml.). The mixture was heated under reflux with stirring for 15 min., then worked up as in the previous experiment to give an orange-yellow solid (1·42 g., 90%) m.p. 63—67°. Sublimation at 80°/14 mm. gave colourless platelets of 5-methyl-3-phenylfuran (1·21 g., 77%), m.p. 66—67·5° (lit.,[16] 60—63°) (Found: C, 83·2; H, 6·3. Calc. for $C_{11}H_{10}O$: C, 83·6; H, 6·3%).

Action of 2N-*Sulphuric Acid–Ethanol on* 3,4-*Epoxy*-3-*phenylbut*-1-*yne*.—The epoxide (0·725 g., 0·005 mole) in ethanol (5 ml.) was mixed with 2N-sulphuric acid (5 ml.) and heated under reflux for 20 min. The clear pale brown solution was cooled and diluted with water, and the oil which separated was extracted into light petroleum (b.p. 40—60°). Work-up as before gave an oil [0·36 g., 38%; 98·5% pure by g.l.c. on column (A)] shown by n.m.r. spectroscopy to be 3-ethoxy-3-phenylbut-1-yn-4-ol (see next experiment). 3-Phenylfuran (0·5%) was also formed (n.m.r. spectroscopy and g.l.c.).

3-*Ethoxy*-3-*phenylbut*-1-*yn*-4-*ol*.—3,4-Epoxy-3-phenylbut-1-yne (0·725 g., 0·005 mole) in ethanol (10 ml.) containing conc. sulphuric acid (2 drops) was heated under reflux for 1·75 hr. The solvent was removed *in vacuo* and the residue treated with water and extracted with light petroleum (b.p. 40—60°). Work-up as in previous experiments gave an oily solid (0·8 g.). Sublimation–distillation (70°/1 mm.) afforded a colourless product (0·59 g.), m.p. 36—41°, which gave 3-*ethoxy*-3-*phenylbut*-1-*yn*-4-*ol* (0·36 g., 38%), m.p. 43·5—44·5° [from cold light petroleum (b.p. 40—60°)], as colourless needles (Found: C, 75·75; H, 7·6. $C_{12}H_{14}O_2$ requires C, 75·8; H, 7·4%), τ (CCl_4) 8·80 ($C\mathit{H}_3{\cdot}CH_2$, 3H, t, *J* 7 c./sec.), 7·50 (HO, 1H, t, *J* 7 c./sec., signal disappeared on deuteriation), 7·33 (H≡C, 1H, s), 6·05—6·99 ($CH_3{\cdot}C\mathit{H}_2$, AB pattern, *J* 9 c./sec., each line split into a quartet, *J* 7 c./sec.), 6·39 ($HOC\mathit{H}_2$, 2H, d, *J* 7 c./sec., collapsed to singlet on deuteriation), and 2·32—2·80 (ArH, 5H, m). In this experiment 3-phenylfuran (0·5%) was identified and estimated by g.l.c.

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[15] R. A. Raphael, 'Acetylenic Compounds in Organic Synthesis,' Butterworth, London, 1955, (a) p. 42; (b) p. 105.

[16] Th. Morel and P. E. Verkade, *Rec. Trav. chim.*, 1951, **70**, 35.

[17] N. M. Klyueva and I. A. Rubtsov, *Biol. Aktivn. Soedinanii Akad. Nauk S.S.S.R.*, 1965, 228 (*Chem. Abs.*, 1965, **63**, 17875b).

3-*Methylbut*-1-*yne*-3,4-*diol*.— 3,4-Epoxy-3-methylbut-1-yne (3·13 g.) was added dropwise to stirred 2N-sulphuric acid (10 ml.) cooled in ice. Stirring was then continued for a further 0·5 hour. The resulting clear yellow solution was continuously extracted with ether for 16 hr., and the extract was dried ($MgSO_4$). Removal of solvent left an oil (3·28 g.) which was distilled *in vacuo* to give the *diol* (2·35 g., 62%), b.p. 89—92°/17 mm., n_D^{21} 1·4658 (Found: C, 57·9; H, 8·4. $C_5H_8O_2$ requires C, 60·0; H, 8·0%). The poor analytical result was explained by the hygroscopic nature of the compound. The i.r. spectrum was consistent with the structure as well as with the presence of water.

Action of 2N-*Sulphuric Acid and Mercuric Sulphate on the Diol*.—3-Methylbut-1-yne-3,4-diol (1·5 g.), 2N-sulphuric acid (15 ml.) and mercuric sulphate (0·15 g.) were stirred together and distilled until no more liquid immiscible with water came over. The organic material was separated and dried ($MgSO_4$) and shown by comparison with authentic material to be 3-methylfuran (0·84 g., 68%, 98·5% pure by g.l.c.).

3,4-*Epoxy*-3-*t*-*butylbut*-1-*yne and* 4-*Chloro*-3*t*-*butylbut*-*yn*-3-ol.—(A. Twamley).—Ethylmagnesium bromide, prepared in tetrahydrofuran (650 ml.) from ethyl bromide (180 g., 1·65 mole) and magnesium (46·2 g., 1·93 g., atom), was converted into ethynylmagnesium bromide by dropwise addition during 3 hr. to a saturated solution of acetylene in tetrahydrofuran (700 ml.) while acetylene (50 l./hr.) was passed continuously through the mixture.

1-Chloro-3,3-dimethylbutan-2-one (147·7 g., 1·1 mole) in tetrahydrofuran (150 ml.) was then added dropwise during 2·5 hr. to the Grignard reagent maintained at 0—5°. The mixture was stirred for 40 hr. at room temperature, cooled to 0°, and decomposed by addition of saturated ammonium chloride solution (200 ml.) during 30 minutes. The salts were filtered off and washed with ether, and the organic filtrate was dried ($MgSO_4$). Removal of solvent left a dark oil which on distillation afforded 3,4-*epoxy*-3-*t*-*butylbut*-1-*yne* (14·5 g., 11%), b.p. 97°/235 mm., n_D^{20} 1·4352 (Found: C, 77·4; H, 9·8. $C_8H_{12}O$ requires C, 77·4; H, 9·9%), and 4-*chloro*-3-*t*-*butylbut*-1-*yn*-3-*ol* (51·8 g., 29%), b.p. 74°/16 mm., n_D^{20} 1·4655 (Found: C, 60·1; H, 8·4; Cl, 21·9. $C_8H_{13}ClO$ requires C, 59·8; H, 8·1; Cl, 22·1%). The chloro-carbinol could be converted into the epoxide by stirring with powdered sodium hydroxide in ether.

4-*Chloro*-3-*phenylbut*-1-*yn*-3-*ol* (A. Twamley).—Ethylmagnesium bromide, prepared in tetrahydrofuran (500 ml.) from ethyl bromide (88·2 g., 0·81 mole) and magnesium (23·3 g., 0·97 g. atom), was converted into ethynylmagnesium bromide by dropwise addition during 2 hr. to a saturated solution of acetylene in tetrahydrofuran (500 ml.).

α-Chloroacetophenone (101·7 g., 0·66 mole) in tetrahydrofuran (100 ml.) was then treated with the Grignard reagent for 1·5 hr. at 0—5° to give the *chlorocarbinol* (31·2 g., 26%), b.p. 63°/0·05 mm., n_D^{20} 1·5579 (Found: C, 66·3; H, 4·9; Cl, 19·3. $C_{10}H_9ClO$ requires C, 66·5; H, 5·0; Cl, 19·7%).

3,4-*Epoxy*-3-*phenylbut*-1-*yne*.— 4-Chloro-3-phenylbut-1-yn-3-ol (180·5 g., 1 mole) in ether (250 ml.) was added dropwise during 1 hr. to a stirred suspension of powdered sodium hydroxide (200 g., 5 moles) in ether (750 ml.). The ether solution was stirred for 5 hr., filtered, and evaporated to leave an oil which, on distillation, afforded 3,4-*epoxy*-3-*phenylbut*-1-*yne* (130 g., 91%), b.p. 68—69°/2 mm., n_D^{19} 1·5430 (Found: C, 83·1; H, 6·1. $C_{10}H_8O$ requires C, 83·4; H, 5·6%).

5-*Chloro*-4-*phenylpent*-1-*yn*-4-*ol* (C. Fake).—Prop-2-ynylmagnesium bromide was prepared in dry ether (600 ml.) from prop-2-ynyl bromide (83·4 g., 0·7 mole) and magnesium (17·3 g., 0·72 g. atom), catalysed by a trace of mercuric chloride. Once reaction had commenced, the mixture was cooled to below −10°. α-Chloroacetophenone (61·8 g., 0·4 mole) in dry benzene (250 ml.) was then added dropwise, with stirring, during 1·5 hr. to the Grignard reagent at −10°. After 3·5 hr. at this temperature the mixture was decomposed with 5N-sulphuric acid (150 ml.) and water (200 ml.), and the ether solution of the product was separated, washed, and dried ($MgSO_4$). Distillation afforded the *chlorocarbinol* (53·9 g., 69%), b.p. 88—89°/0·15 mm., n_D^{20} 1·5559 (Found: C, 68·1; H, 5·6; Cl, 17·9. $C_{11}H_{11}ClO$ requires C, 67·9; H, 5·7; Cl, 18·25%).

4,5-*Epoxy*-4-*phenylpent*-1-*yne* (C. Fake).—5-Chloro-4-phenylpent-1-yn-4-ol (40·33 g., 0·21 mole) in ether (250 ml.) was added dropwise during 15 min. to a suspension of powdered sodium hydroxide (42·0 g., 1·05 mole) in ether (400 ml.). The ether solution was stirred for 5·5 hr., filtered, and evaporated, and the residue was distilled *in vacuo* to give 4,5-*epoxy*-4-*phenylpent*-1-*yne* (24·5 g., 75%), b.p. 64·5—68°/0·13 mm., n_D^{16} 1·5420 (Found: C, 83·8; H, 6·3. $C_{11}H_{10}O$ requires C, 83·5; H, 6·3%).

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