Synthesis of Aryl and Heterocyclic Acetylenes *via* Copper Acetylides

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Ethynylbenzene (I), 1-ethynylnaphthalene (IX), 2-ethynylthiophen (IV), and 2-ethynyl-5-iodothiophen (XII) have been prepared from the corresponding iodo-derivatives (V), (VII), (II), and (X), by reaction with copper(I) 3,3-diethoxyprop-1-ynide to give αβ-acetylenic aldehydes, followed by base-catalysed deformylation. Alternatively, copper(I) 3-tetrahydropyranyloxy-prop-1-ynide gave the αβ-acetylenic alcohols (XVIII), (XIX), (XIII), (XX), and (XV), which were oxidised with nickel peroxide and then deformylated, or oxidised in aqueous alkali directly, to the same acetylenes (I), (IX), (IV), (XII), and 5-ethynyl-2,2′-bithienyl (XVII). The application of this sequence to the protection of terminal ethynyl groups is indicated.

MONOSUBSTITUTED aryl and heterocyclic acetylenes have previously been prepared from appropriate dihalogeno-derivatives by elimination with strong bases,[1,2] by decarboxylation[3] of αβ-acetylenic acids prepared by several routes,[4] and by alkaline cleavage of β-chloroacroleins.[5] Most of these methods require vigorous conditions.

The reaction of an aromatic[6] or heterocyclic[7] iodo-compound (R^1I), with a copper(I) acetylide ($CuC{:}C{\cdot}R^2$) in an inert atmosphere to give the corresponding disubstituted acetylene ($R^1{\cdot}C{:}C{\cdot}R^2$) has now been considerably extended and numerous examples have been summarised.[8] In an earlier report[9] we indicated how this reaction could be used for the synthesis of unsubstituted aryl and heterocyclic acetylenes, and we now describe further details.

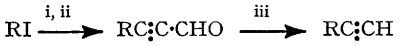
Monosubstituted acetylenes cannot be prepared by this general method since monocopper(I) acetylide is unknown, but a substituted copper(I) acetylide with a readily removable substituent acting as a 'protecting group' would be satisfactory.

The base-catalysed deformylation of αβ-acetylenic aldehydes with aqueous alkali was first described by

[1] T. F. Rutledge, 'Acetylenic Compounds,' Reinhold, New York, 1968, p. 24.
[2] T. L. Jacobs, 'Organic Reactions,' John Wiley and Sons, New York, 1949, vol. V, p. 1.
[3] A. W. Johnson, 'Chemistry of Acetylenic Compounds,' Edward Arnold, 1950, vol. II, p. 166.
[4] T. F. Rutledge, 'Acetylenic Compounds,' Reinhold, New York, 1968, p. 32.
[5] K. Bodendorf and R. Mayer, *Chem. Ber.*, 1965, **98**, 3554.
[6] R. D. Stephens and C. E. Castro, *J. Org. Chem.*, 1963, **28**, 3313.
[7] R. E. Atkinson, R. F. Curtis, and G. T. Phillips, *Chem. and Ind.*, 1964, 2101.
[8] A. M. Sladkov and L. Yu. Ukhin, *Uspekhi Khim.*, 1968, **37**, 1750.
[9] R. E. Atkinson, R. F. Curtis, D. M. Jones, and J. A. Taylor, *Chem. Comm.*, 1967, 718.

Claisen [10] for prop-2-ynal and 3-phenylprop-2-ynal and was later reported for oct-2-ynal [11] and but-2-ynal.[12] Apart from a very recent related example [13] this reaction has not been further explored although the formation of ethynylbenzene (I) from benzoylphenylacetylene by reaction with sodamide is probably an analogous reaction.[14]

The sequence of reactions in Scheme 1 was therefore investigated. The iodo-compounds (II), (V), (VII), and (X) were treated with copper(I) 3,3-diethoxyprop-1-ynide and the products were hydrolysed to give the aldehydes (III), (VI), (VIII), and (XI). Aqueous methanolic 4N-sodium hydroxide at 50° produced smooth deformylation to give the corresponding acetylenes (IV), (I), (IX), and (XII).

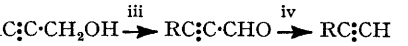


R	RI	RC:C·CHO	RC:CH
2-Thienyl	(II)	(III)	(IV)
Phenyl	(V)	(VI)	(I)
1-Naphthyl	(VII)	(VIII)	(IX)
5-Iodo-2-thienyl	(X)	(XI)	(XII)

SCHEME 1

Reagents: i, CuC·C:CH(OEt)$_2$; ii, H$^+$; iii, OH$^-$.

However, the consistent preparation of these highly reactive aldehydes by this method presents some difficulties which were removed by the sequence illustrated in Scheme 2. Copper(I) tetrahydropyranyloxyprop-1-ynide with the iodo-compounds (II), (XIV), (V), (VII), and (X) gave, after hydrolysis, the alcohols (XIII), (XV), (XVIII), (XIX), and (XX) respectively in good yield. Nickel peroxide in benzene has been used [15] for the oxidation of benzylic and primary allylic hydroxy-functions to the corresponding aldehydes and when the above alcohols were oxidised in this way at 50° high yields of the aldehydes (III), (XVI), (VI), (VIII) and (XI) were obtained. These could then be deformylated as above.



	RI	RC:C·CH$_2$OH	RC:C·CHO	RC:CH
2-Thienyl	(II)	(XIII)	(III)	(IV)
2,2′-Bithienyl-5-yl	(XIV)	(XV)	(XVI)	(XVII)
Phenyl	(V)	(XVIII)	(VI)	(I)
1-Naphthyl	(VII)	(XIX)	(VIII)	(IX)
5-Iodo-2-thienyl	(X)	(XX)	(XI)	(XII)

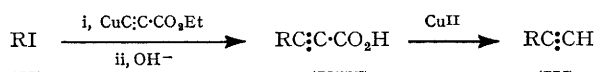
(THP = Tetrahydropyranyl)

SCHEME 2

Reagents: i, CuC:C·CH$_2$·OTHP; ii, H$^+$; iii, NiO$_2$–PhH; iv, OH$^-$.

Direct production of the same acetylenes was achieved by oxidation with nickel peroxide in aqueous methanolic 2N-sodium hydroxide at 50°; this proceeded *via* deformylation, rather than decarboxylation, since the corresponding acids were unchanged under these conditions.

Copper-catalysed decarboxylation of αβ-acetylenic acids under less vigorous conditions has been described [16,17] and this suggested a further alternative (Scheme 3). However, synthesis of β-(2-thienyl)-propiolic acid (XXI) from 2-iodothiophen (II) and the copper(I) salt of ethyl propiolate was only achieved in comparatively low yield. In addition the preparation of the copper(I) salt presented difficulties and this method was not further investigated.



R = 2-thienyl

SCHEME 3

The mechanism of this deformylation has not been investigated. A similar reaction in aliphatic aldehydes with two or three electron-withdrawing substituents in the α-position, *e.g.*, trichloroacetaldehyde, is well known; a mechanism has been proposed [18] after an investigation of the kinetics of the reaction. A mechanism has also been suggested for the deformylation of but-2-ynal [19] and a related mechanism for the alkaline cleavage of β-chloroacroleins [5] but no kinetic evidence is available.

When this work was carried out only two other protecting groups for terminal acetylenes were available, *i.e.* –Cl [20] and –CO$_2$H and removal of these groups required vigorous reduction in the former, and elevated temperature,[17] in the latter case. The present reaction sequence emphasises the possibility of using the formyl group, for the protection of terminal ethynyl groups. The formylation of a terminal acetylene can easily be achieved, *e.g.* conversion to an acetylenic Grignard followed by reaction with orthoformic ester [21] or direct formylation under Vilsmeier-Haack conditions [22] (a reaction which has hardly been explored), give good yields of αβ-acetylenic aldehydes.

Simultaneously with our earlier publication [9] protection of terminal ethynyl groups by trimethylsilylation was reported; [23] the synthetic possibilities and some of the limitations of the latter approach have been demonstrated.[24]

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EXPERIMENTAL

M.p.s were determined on a Kofler hot-stage apparatus; u.v. spectra were measured on a Unicam SP 800 spectrophotometer in methanol and i.r. spectra were determined for potassium bromide discs or films with Perkin-Elmer spectrophotometers (Models 257 and 457). ^{1}H N.m.r. spectra were determined at 60 Mc./sec. in carbon disulphide solution with a Perkin-Elmer R10 spectrometer. System I of our earlier publication [25] was used for t.l.c. Silicagel was 200—300 mesh (Koch-Light and Co., Ltd.), alumina was Spence H, acid-washed to neutrality and activated at 100° for 10 hr. Our general procedure for couplings with copper(I) acetylides has been described in detail.[25,26]

Preparation of Prop-2-ynal Derivatives by Direct Method (*Scheme* 1).—(a) 3-*Phenylprop-2-ynal* (VI). Copper(I) 3,3-diethoxyprop-1-ynide (10·9 g.), pyridine (100 ml.), and iodobenzene (11·0 g.) were heated under reflux for 7 hr. Work-up under neutral conditions, chromatography over alumina and elution with pentane gave the diethylacetal of (VI) as an oil, (4·6 g.), b.p. 110—112°/0·5 mm., (lit.,[27] 153—156°/19 mm.), identical with an authentic sample. Acid hydrolysis [27] gave the aldehyde (VI), b.p. 60°/0·1 mm. (lit.,[27] 114—117°/17 mm.).

(b) 3(1-*Naphthyl*)*prop*-2-*ynal* (VIII). Copper(I) 3,3-diethoxyprop-1-ynide (1·5 g.), pyridine (70 ml.), and 1-iodonaphthalene (2·0 g.) were heated under reflux for 4 hr. The reaction mixture was worked up to give the crude diethyl acetal of (VIII) as a brown oil (1·43 g.). This was heated with water (10 ml.), sulphuric acid (*d* 1·84; 2 ml.) and a few drops of methanol on a steam-bath for 30 min.; the mixture was then extracted with ether to give the *aldehyde* (VIII) as a pale yellow oil, (0·70 g.), b.p. 85° (bath temp.)/0·5 mm. (Found: C, 86·2; H, 4·8. $C_{13}H_8O$ requires C, 86·6; H, 4·5%), $\lambda_{max.}$ 230, 246, 322, 339 mμ (log ε 4·26, 4·14, 4·01, 3·99); $\nu_{max.}$ 2200 (C≡C), 1650 cm.$^{-1}$ (CHO); τ, 0·48 (l, s, C*H*O), 1·7 (complex 1H, naphthalene-2*H*), 2·0—2·8 (complex multiplet, 6H, naphthalene protons).

3-(2-Thienyl)prop-2-ynal (III) and 3-(2-iodo-5-thienyl)-prop-2-ynal (XI) were prepared as already described.[25]

Preparation of Prop-2-ynal Derivatives (*Scheme* 2).—(a) 3-*Phenylprop*-2-*ynol* (XVIII).—Copper(I) 3-tetrahydropyranyloxyprop-1-ynide (12·5 g.), pyridine (200 ml.), and iodobenzene (10·0 g.) were heated under reflux for 10 hr. Work-up under neutral conditions, with chromatography over alumina and elution with pentane, gave the *tetrahydropyranyl ether* as a pale-yellow oil, (5·9 g.), b.p. 132°/0·8 mm., n_D^{18} 1·5455 (Found: C, 77·7; H, 7·5. $C_{14}H_{16}O_2$ requires C, 77·8; H, 7·5%), $\lambda_{max.}$ 242, 251 mμ (log ε 4·04, 3·96), $\nu_{max.}$ 2220 (C≡C); τ, 2·6 (s, 5H, phenyl protons), 5·05 (t, 1H, −O−C*H*−O), 5·5 (s, 2H, C≡C−CH_2), 6·3 (t, 2H, OCH_2), 8·3 (s, 6H, CH_2−CH_2−CH_2). Hydrolysis with methanolic 2N-sulphuric acid gave the alcohol (XVIII), b.p. 97°/0·3 mm., n_D^{18} 1·5815 (lit.,[28] b.p. 103—105°/1·5 mm., n_D^{18} 1·5820).

(b) 3-(1-*Naphthyl*)*prop*-2-*ynol* (XIX).—In an identical sequence copper(I) 3-tetrahydropyranyloxyprop-1-ynide (6·1 g.) and 1-iodonaphthalene (7·25 g.) in pyridine (75 ml.) were heated for 5 hr. to give a crude product (6·0 g.), this was hydrolysed and worked up to give an oil (3·9 g.). Chromatography of this over alumina and elution with pentane gave 1-iodonaphthalene (2·25 g.); further elution with pentane–ether (10 : 1) gave the *alcohol* (XIX) (1·48 g.) from the ether–pentane as needles, m.p. 44—45·5° (Found: C, 85·8; H, 5·4. $C_{13}H_{10}O$ requires C, 85·7; H, 5·5%); $\lambda_{max.}$ 234, 286, 298, 307, 311 mμ (log ε 4·37, 3·99, 4·12, 3·96 and 3·98), $\nu_{max.}$ 3350 (OH), 2200 cm.$^{-1}$ (C≡C); τ 1·6 (complex, 1H, naphthalene-2-H), 2·10—2·75 (m, 6H, naphthalene protons), 5·40 (s, 2H, CH_2), 6·80 (s, 1H, O*H*).

(c) 3(2-*Iodo*-5-*thienyl*)*prop*-2-*ynol* (XX). In the same way, copper(I) 3-tetrahydropyranyloxyprop-1-ynide (20·2 g.) and 2,5-di-iodothiophen (33·6 g.) in pyridine (250 ml.) were heated for 5 hr. Work up gave a crude product which was chromatographed on silica gel (1 kg.). Elution with pentane–ether (10 : 1) gave 2,5-di-iodothiophen (13·5 g.) and then the tetrahydropyranyl ether (9·2 g.). Hydrolysis, followed by chromatography over alumina (450 g.) with elution by pentane–ether (8 : 1) gave the *alcohol* (XX) (4·6 g.) as needles, m.p. 58° (from pentane) (Found: C, 31·4; H, 2·3. C_7H_5IOS requires C, 31·6; H, 1·9%), $\lambda_{max.}$ 284 mμ (log ε 4·17), $\nu_{max.}$ 3250, 1010 (OH); 2210, (C≡C), 790 cm.$^{-1}$ (thiophen-2,5-diyl); τ, 2·91 (d, 1H, *J* 3·6, thiophen-3-H), 3·16 (d, 1H, thiophen-4-H), 5·51 (s, 2H, CH_2), 8·02 (s, 1H, O*H*).

3-(2-Thienyl)prop-2-ynol (XIII) [25] and 5-(3-hydroxyprop-1-ynyl)-2,2′-bithienyl (XV) [29] were prepared as already described.

Oxidation of Prop-2-ynol Derivatives with Nickel Peroxide.—The ratio of nickel peroxide (B.D.H.) to substrate and solvent was not critical. The following description is typical.

(a) 5-(*Prop*-3-*al*-1-*ynyl*)-2,2′-*bithienyl* (XVI).—Nickel peroxide (1·5 g.) was added to a solution of 5-(3-hydroxyprop-1-ynyl)-2,2′bithienyl (XV) (332 mg.), in benzene (5 ml.) and the heterogeneous mixture was stirred at 50° (with control by t.l.c.) until all the alcohol had been oxidised (1 hr.). The solid was collected and washed with dry methanol (10 ml.); the combined organic layers were evaporated under reduced pressure. The residue was crystallised from pentane to give 5-(prop-3-al-1-ynyl)-2,2′-bithienyl (XVI) (235 mg.) as pale yellow needles, m.p. 66°, identical with authentic material.[29]

In the same way the following alcohols were converted into the corresponding aldehydes identical with authentic samples in the yields stated: (b) 3-Phenylprop-2-ynol (XVIII) gave 3-phenylprop-2-ynal (VI) [27] (70%); (c) 3-(1-naphthyl)prop-2-ynol (XIX) gave 3-(1-naphthyl)-prop-2-ynal (VIII); see above (81%); (d) 3-(2-Thienyl)-prop-2-ynol (XIII) gave 3-(2-thienyl)prop-2-ynal (III),[25] (74%); (e) 3-(2-iodo-5-thienyl)prop-2-ynol (XX) gave 3-(2-iodo-5-thienyl)prop-2-ynal (XI) [25] (80%).

Deformylation of αβ-*Acetylenic Aldehydes to Acetylenes.*—The concentration of alkali was not critical; the following description is typical.

(a) 1-*Ethynylnaphthalene* (IX). The aldehyde (VIII) (170 mg.) in methanol (4 ml.) and 4N-sodium hydroxide (4 ml.) was warmed at 50° for 1 hr. (with control by t.l.c.). Water was added and the product was worked up with ether to give the acetylene (IX) as an oil (130 mg.), b.p. 45° (block temp.)/0·25 mm., n_D^{20} 1·6360 (lit.,[30] b.p. 92°/4 mm.,

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[30] D. Bertin, *Compt. rend.*, 1949, **229**, 660.

n_D^{20} 1·6360), $\lambda_{max.}$ 235, 285, 296, 307 mμ (log ε 4·18, 3·84, 3·96, 3·79), $\nu_{max.}$ 3300 (C≡CH), 2100 cm (C≡C), τ, 1·5 (complex, 1H, naphthalene-2-*H*), 2·0—2·6 (m, 6H, naphthalene protons), 6·61 (s, 1H, C≡C*H*).

(b) 2-*Iodo*-5-*ethynyl thiophen* (XII). In the same way the aldehyde (XI) (130 mg.) gave 2-iodo-5-ethynylthiophen (XII), as a pale yellow oil, (98 mg.) which was characterised as the *mercury* derivative; this was obtained as microcrystals from ethanol, m.p. 201—203° (decomp.) (Found: C, 21·8; H, 0·9. $C_{12}H_4HgI_2S_2$ requires C, 21·6; H, 0·6%); $\nu_{max.}$ 2140 (C≡C), 790 cm.$^{-1}$ (thiophen-2,5-diyl).

In addition the following aldehydes gave the corresponding acetylenes in the yields stated and identical with authentic samples: 3-Phenylprop-2-ynal (VI) gave ethynylbenzene (I) (87%); 3-(2-thienyl)prop-2-ynal (III) gave ethynylthiophen (IV) (80%);[31] 5-(prop-3-al-1-ynyl)-2,2′-bithienyl (XVI) gave 5-Ethynyl-2,2′-bithienyl (XVII) (90%).[32]

Direct Conversion of αβ-Acetylenic Alcohols into Acetylenes.—The following is typical. 5-(3-Hydroxyprop-1-ynyl)-2,2′-bithienyl (XV) [29] (80 mg.) in methanol (0·1 ml.) was added to a suspension of nickel peroxide (780 mg.) in N-sodium hydroxide (1 ml.) and stirred at 50°, (with control by t.l.c.) for 3 hr. The product was diluted, filtered, and the filtrate was extracted with ether to give 5-ethynyl-2,2′-bithienyl (44 mg., 63%), identical with the sample above.

Phenylacetylene (52%), 1-ethynylnaphthalene (41%), and 2-ethynylthiophen (50%), were also prepared in the same way.

β-(2-*Thienyl*)*propiolic acid* (XXI).—The copper(I) derivative (906 mg.) of ethyl propiolate and 2-iodothiophen (1·03 g.) in pyridine (50 ml.) were heated under reflux for 8 hr. and then worked up to give the crude ethyl ester. Hydrolysis with 1·5N-sodium hydroxide and work up gave the acid (XXI) (452 mg.) as needles from pentane–ether, m.p. 132—133° (lit.,[33] 130—131°) identical with an authentic sample.

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