Pergamon

Tetrahedron 57 (2001) 9475–9480

TETRAHEDRON

A convenient and highly regio and stereoselective method for the synthesis of (*E*)-3-alkylidene isobenzofuran-1(3*H*)-ones (phthalides)

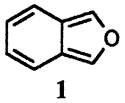
Rupa Mukhopadhyay and Nitya G. Kundu*

Department of Organic Chemistry, Indian Association for the Cultivation of Science, Jadavpur, Calcutta 700 032, India

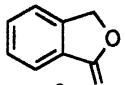
Received 5 June 2001; revised 29 August 2001; accepted 20 September 2001

Abstract—2-Iodobenzyl alcohol on treatment with acetylenic carbinols in the presence of a palladium catalyst and copper(I) iodide as a co-catalyst afforded disubstituted alkynes. Jones oxidation of the disubstituted alkynes led to (*E*)-3-alkylidene isobenzofuran-1(3*H*)-ones in good yields in a highly regio and stereoselective manner. The *E*-isomers were obtained exclusively instead of the more stable *Z*-isomers.

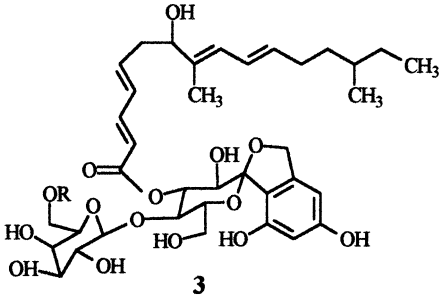
Isobenzofuran (IBF) **1** and Isobenzofuran-1(3*H*)-one (phthalide) **2** are integral parts of many naturally occurring substances.[1–6] For example, the papulacandins **3** are a group of antifungal agents from Papularia Spherosperma which exhibit potent in vitro activity against Candida albicans and related microorganisms.[7–9] Recently, the common opportunistic infection in AIDS patients, pneumocystis carvini pneumonia has been effectively overcome by new members of the papulacandin family, e.g. **3d** (Mer-WF 3010) and **3e** (L-687-781).[10] Similarly, isobenzofuran-1(3*H*) ones (phthalides) possess a wide range of medicinal properties.[11]



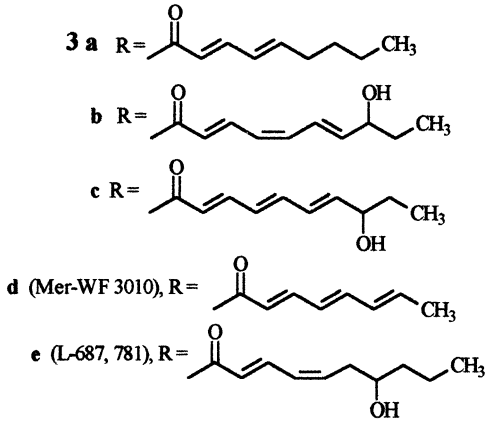
1



2



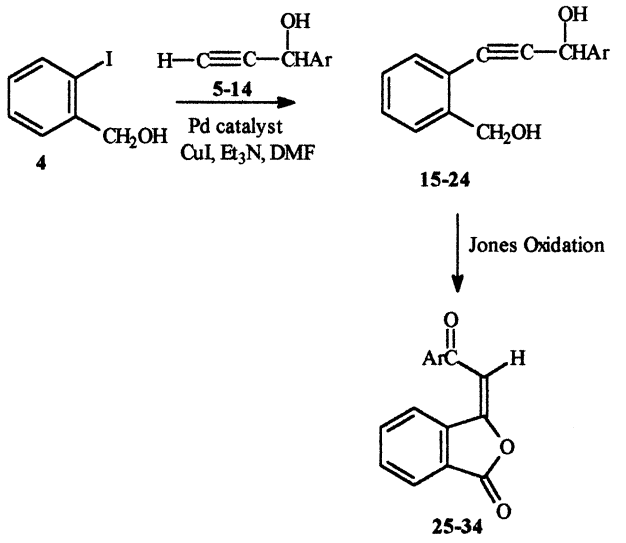
3



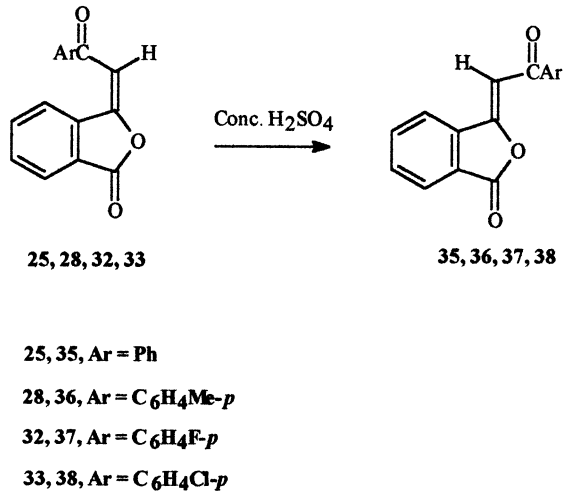
In view of their importance, various methods have been developed previously for the synthesis of isobenzofuran-1(3*H*)-ones (phthalides).[12] However, only a few palladium mediated syntheses of isobenzofuran-1(3*H*)ones (phthalides) were reported.[13] In recent years, we have developed methods for the synthesis of various benzofused heterocyclic compounds e.g. benzofurans,[14] phthalides,[13] quinolines and quinolones,[15] 1,4-benzodioxanes,[16] 3,4-dihydro-2*H*-1,4-benzoxazines,[17] isoindolinones,[18] flavones and flavanones,[19] benzodioxepinones and benzoxazepinones,[20] and benzothiazolines[21] by palladium catalysed reactions with terminal alkynes.[22] Because of the biological importance of the isobenzofuran-1-(3*H*)ones and the lack of many convenient palladium catalysed procedures for their synthesis, we were prompted to develop a general and efficient method for the synthesis of isobenzofuran-1-(3*H*)-ones starting from 2-iodobenzyl alcohol and acetylenic carbinols. With that purpose, we reacted 2-iodobenzyl alcohol **4** with

Keywords: alkynes; isobenzofuran-1(3*H*)ones; palladium catalysis.
* Corresponding author. Tel.: +91-33-473-4971; fax: +91-33-473-2805; e-mail: ocrm@mahendra.iacs.res.in

0040–4020/01/$ - see front matter
PII: S0040-4020(01)00943-7



Scheme 1.



Scheme 2.

acetylenic carbinols **5**–**14** with a terminal alkyne functionality in the presence of a palladium catalyst and cuprous iodide as a co-catalyst.[22c,f] The reactions were usually carried out by stirring a mixture of 2-iodobenzyl alcohol **4** (1 mmol) and acetylenic carbinols **5**–**14** (1.5 mmol) in DMF and Et_3N in the presence of bis(triphenylphosphine)-palladium(II)chloride (5 mol%), copper(I)iodide (8 mol%) at room temparature for 24 h. It was observed that the disubstituted alkynes (**15**–**24**) were the major products[23b] (Scheme 1 and Table 1).

The structures of the acyclic products (disubstituted alkynes) **15**–**24** follow from their analytical and spectroscopic data. In the ^{1}H NMR, the benzylic $-CH_2-$ group could be seen at δ 4.7–4.8 and the CHOH at δ 5.55–5.87 as singlets. In the ^{13}C NMR, peaks at δ 94 and 84 (C≡C), 65.3 (CHOH) and 63.9 (CH_2) were confirmative of the structures of the disubstituted alkynes. We have also used other palladium-catalysed conditions for the reactions of 2-iodobenzyl alcohol with acetylenic carbinols but have obtained the disubstituted alkynes in poor yields only or not at all. For example, with $PdCl_2(PPh_3)_2$ (3.5 mol%), CuI (8 mol%), Et_3N (4 equiv.), DMF at 80°C for 24 h, only 15–20% of the disubstituted alkynes could be obtained. Similarly, the use of $Pd(OAc)_2$ (5 mol%), K_2CO_3 (5 equiv.) and Bu_4NBr (0.5 equiv.) in DMF at rt for 24 h. did not give any products.

Interestingly it was observed that the compounds **15**–**24** were smoothly oxidised using Jones oxidation to yield the 3-alkylidene isobenzofuran-1(3*H*)ones (phthalides) **25**–**34** in excellent yields. The structures of compounds **25**–**34** as phthalides follow from their analytical and spectroscopic data. In IR, the presence of absorption at 1799–1786 cm^{-1} indicated the γ-lactone ring, whereas a vinylic hydrogen could be seen at δ 7.21–6.94 in the ^{1}H NMR spectra. The isobenzofuran-1(3*H*)ones were given the *E*-stereochemistry on the basis of the presence of a downfield proton at δ 9.03–8.96, which was assigned to the C-4 aromatic hydrogen which was shifted downfield due to the proximity of the aroyl group. For the corresponding isobenzofuran-1(3*H*)ones (phthalides) of *Z*-stereochemistry, the aromatic signals were seen between δ 7.3–8.2.[24–26] Also, for *Z*-isobenzofuranones (phthalides) **35**–**38** the vinylic hydrogen was at higher field (δ 6.70–6.78) compared to the vinylic hydrogens of *E*-isobenzofuranones **25**–**34** which were at δ 7.21–6.94 due to the deshielding effect of the ring oxygen. The *E*-configuration of compounds **25**–**34** also follows from their conversion to the corresponding isobenzofuranones of *Z*-configuration by treatment with

Table 1. Palladium-catalysed reactions of 2-iodobenzyl alcohol **4** with acetylenic carbinols **5**–**14** and subsequent Jones oxidation of the products **15**–**24** to 3-alkylidene isobenzofuran-1(3*H*)ones (phthalides) **25**–**34**

Entry	Acetylenic carbinols (**5**–**14**)	Disubstituted alkynes[a] (%) (**15**–**24**)	Isobenzofuran-1(3*H*)-ones[b] (%) (**25**–**34**)
1.	**5**, C_6H_5	**15**, (60)	**25**, (49)
2.	**6**, C_6H_4Me-*o*	**16**, (73)	**26**, (45)
3.	**7**, C_6H_4Me-*m*	**17**, (60)	**27**, (40)
4.	**8**, C_6H_4Me-*p*	**18**, (56)	**28**, (51)
5.	**9**, C_6H_4OMe-*o*	**19**, (58)	**29**, (52)
6.	**10**, C_6H_4OMe-*m*	**20**, (69)	**30**, (50)
7.	**11**, C_6H_4OMe-*p*	**21**, (56)	**31**, (50)
8.	**12**, C_6H_4F-*p*	**22**, (50)	**32**, (52)
9.	**13**, C_6H_4Cl-*p*	**23**, (56)	**33**, (48)
10.	**14**, 3,4-methylene dioxy-phenyl	**24**, (75)	**34**, (40)

[a] Yields are based on 2-iodobenzylalcohol.
[b] Yields are based on the corresponding disubstituted alkynes.

sulphuric acid (see Scheme 2 and Section 1). Though the *Z*-isomer is more stable than the corresponding *E*-isomer, we got exclusively the isobenzofuran-1-ones **25**–**34** of *E*-configuration from the Jones oxidation of the corresponding disubstituted alkynes **15**–**24**.

In conclusion, we have described a very convenient and general method for the synthesis of (*E*)-3-alkylidene-isobenzofuran-1-(3*H*)-ones (phthalides). The method is characterised by (i) easy availability of inexpensive starting materials, (ii) use of non-toxic reagents and (iii) simple operational procedures (a two step reaction). The present method is complementary to the method which we have described for the synthesis of (*Z*)-3-alkylidene-isobenzofuran-1-(3*H*)-ones.[13]

1. Experimental

1.1. General

Melting points were determined in open capillary tubes on Gallenkamp (England) and in sulphuric acid bath and on a Reichert (285980) (Austria) melting point apparatus and are uncorrected. UV spectra were recorded on a Hitachi 200-20 spectrometer using spectrophotometric grade ethanol (Baker). IR spectra were taken on a Perkin–Elmer 298 instrument for samples as KBr plates or liquid films. ^{1}H NMR spectra were recorded on a Varian EM-360, a Varian XL-200 and a Bruker DPX-300 spectrometer for samples as indicated with tetramethylsilane as internal reference. ^{13}C Spectra (75.5 MHz) were obtained on a Bruker DPX-300 spectrometer. Chemical shifts are reported in δ unit (ppm); *J* values given in Hz; splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet, m, multiplet; and br, broad. Analytical thin-layer chromatography (TLC) was performed on precoated 0.2 mm. silica gel 60F-254 (E. Merck), and the spots were visualised with UV light. Column chromatography was done on silica gel (60–120 mesh) or neutral alumina. Elemental analyses (C, H, N) were carried out on Perkin–Elmer 240C analyser. 2-Iodobenzylalcohol and palladium catalyst were commercially available (Aldrich Chem. Co.). Acetylenic carbinols were synthesised by the procedure of Jones et al.[28] starting from the corresponding aldehyde.

1.2. Synthesis of disubstituted alkynes 15–24

General procedure: A mixture of 2-iodobenzyl alcohol **4** (1 mmol), bis(triphenylphosphine) palladium(II)chloride (5 mol%), CuI (8.0 mol%) in triethylamine (5 mL) and DMF (2.5 mL) was stirred under nitrogen atmosphere for 1 h. Then acetylenic carbinol **5**–**14** (1.2–1.5 mmol) was added to the reaction mixture. The solution was stirred at rt for 24 h. Then the mixture was evaporated to dryness under reduced pressure and the residue was extracted with chloroform (3×50 mL). The combined organic layers were washed with distilled water (3×50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under low pressure to give a residue. The crude mass was purified by column chromatography on neutral alumina to afford the pure disubstituted alkyne **15**–**24** using 50% ethyl acetate in petroleum ether (60–80°C) as the eluent. Finally the product were crystallised from $CHCl_3$.

1.2.1. 2-(3-Hydroxy-3-phenyl)-prop-1-ynyl benzyl alcohol 15. White powder ($CHCl_3$), mp 98°C. IR (KBr): ν= 3265, 1600, 1490, 1479, 1446 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.25–7.60 (m, 9H, Ar–H), 5.68 (s, 1H, CHOH), 4.78 (s, 2H, –CH_2). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ= 142.9, 132.8, 129.4, 129.1, 128.9, 128.0, 127.9, 127.0, 94.0, 84.1, 65.4, 64.3. UV (EtOH): λ_{max} (log ε)=254 (4.11), 245 (4.18), 211 (4.36). Anal. Calcd for $C_{16}H_{14}O_2$:C, 80.67; H, 5.88. Found: C, 80.34; H, 5.65.

1.2.2. 2-[3-Hydroxy-3-(*o*-methylphenyl)]-prop-1-ynyl benzyl alcohol 16. White powder ($CHCl_3$+light petroleum ether), mp 134°C. IR (KBr) ν=3294, 3138, 1602,1483, 1461 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$+DMSO-d_6): δ= 7.20–7.73 (m, 8H, Ar–H), 5.87 (s, 1H, CHOH), 4.80 (s, 2H, –CH_2), 2.50 (s, 3H, CH_3). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=143.5, 139.3, 135.5, 132.4, 130.9, 129.0, 128.6, 127.4, 126.4, 126.3, 126.2, 125.9, 93.4, 83.0, 64.5, 62.9, 18.9. UV (EtOH): λ_{max} (log ε)=287 (2.88), 255 (4.26), 246 (4.32), 212 (4.47). Anal. Calcd for $C_{17}H_{16}O_2$: C, 80.95; H, 6.35. Found: C, 80.72; H, 6.71.

1.2.3. 2-[3-Hydroxy-3-(*m*-methyl phenyl)]-prop-1-ynyl benzyl alcohol 17. White solid ($CHCl_3$), mp 79°C. IR (KBr): ν=3267, 3128, 1604, 1481, 1446 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.08–7.41 (m, 8H, Ar–H), 5.55 (s, 1H, CHOH), 4.69 (s, 2H, CH_2), 2.32 (s, 3H, –CH_3). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ=145.1, 143.2, 141.0, 135.0, 131.9, 131.5, 131.2, 130.5, 130.2, 130.1, 126.4, 123.9, 96.5, 86.5, 67.3, 66.3, 24.1. UV (EtOH): λ_{max} (log ε)= 287 (2.75), 254 (4.23), 246 (4.29), 212 (4.44). Anal. Calcd for $C_{17}H_{16}O_2$: C, 80.95; H, 6.35. Found: C, 80.76; H, 6.56.

1.2.4. 2-[3-Hydroxy-3-(*p*-methyl phenyl)]-prop-1-ynyl benzyl alcohol 18. White powder ($CHCl_3$+light petroleum ether), mp 117°C. IR (KBr): ν=3307, 3188, 1512, 1477, 1450, 1417 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.19–7.50 (m, 8H, Ar–H), 5.66 (s, 1H, CHOH), 4.79 (s, 2H, –CH_2), 2.36 (s, 3H, CH_3). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ=142.6, 138.4, 137.7, 132.4, 129.4, 129.0, 127.6, 126.6, 120.9, 93.9, 84.0, 65.0, 63.9, 21.2. UV (EtOH): λ_{max} (log ε)=254 (4.22), 245 (4.28), 211 (4.29). Anal. Calcd for $C_{17}H_{16}O_2$: C, 80.95; H, 6.35. Found: C, 80.60; H, 6.40.

1.2.5. 2-[3-Hydroxy-3-(*o*-methoxy phenyl)]-prop-1-ynyl benzyl alcohol 19. Colourless small needles ($CHCl_3$), mp 106°C. IR (KBr): ν=3271, 1602, 1589, 1494, 1465, 1440 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ=6.88–7.58 (m, 8H, Ar–H), 5.88 (s, 1H, CHOH), 4.73 (s, 2H, –CH_2), 3.86 (s, 3H, –OCH_3). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ= 157.0, 143.2, 132.7, 130.2, 129.2, 129.1, 128.3, 127.9, 127.8, 121.5, 121.4, 111.3, 93.9, 83.8, 64.2, 62.0, 56.0. UV (EtOH): λ_{max} (log ε)=274 (3.58), 246 (4.21), 211 (4.43). Anal. Calcd for $C_{17}H_{16}O_3$: C, 76.11; H, 5.97. Found: C, 75.72; H, 6.04.

1.2.6. 2-[3-Hydroxy-3-(*m*-methoxy phenyl)]-prop-1-ynyl benzyl alcohol 20. White solid ($CHCl_3$), mp 90°C. IR (KBr): ν=3251, 3116, 1606, 1587, 1485, 1452,

1433 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=6.79–7.39 (m, 8H, Ar–H), 5.55 (s, 1H, CHOH), 4.68 (s, 2H, $-CH_2$), 3.73 (s, 3H, $-OCH_3$). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ= 160.1, 142.8, 132.7, 130.0, 129.3, 128.3, 127.9, 121.6, 119.5, 114.4, 113.6, 112.4, 94.1, 84.3, 65.0, 63.9, 55.6. UV (EtOH): λ_{max} (log ε)=275 (3.50), 246 (4.25), 211 (4.47). Anal. Calcd for $C_{17}H_{16}O_3$:C, 76.11; H, 5.97. Found: C, 76.34; H, 6.26.

1.2.7. 2-[3-Hydroxy-3-(*p*-methoxy phenyl)]-prop-1-ynyl benzyl alcohol 21. White solid ($CHCl_3$), mp 102°C. IR (KBr): ν=3363, 3066, 1610, 1510, 1483, 1452, 1419 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=6.78–7.45 (m,, 8H, Ar–H), 5.54 (s, 1H, CHOH), 4.73 (s, 2H, $-CH_2$), 3.73 (s, 3H, $-OCH_3$). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=160.0, 142.8, 133.4, 132.7, 129.2, 128.5, 128.2, 127.8, 121.6, 114.3, 94.3, 84.2, 64.7, 63.9, 55.7. Anal. Calcd for $C_{17}H_{16}O_3$: C, 76.11; H, 5.97. Found: C, 75.92; H, 5.73.

1.2.8. 2-[3-Hydroxy-3-(*p*-fluoro phenyl)]-prop-1-ynyl benzyl alcohol 22. White solid ($CHCl_3$+light petroleum ether), mp 104°C. IR (KBr): ν=3263, 3116, 1604, 1506, 1479, 1448, 1407 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ= 7.07–7.56 (m, 8H, Ar–H), 5.66 (s, 1H, CHOH), 4.78 (s, 2H, $-CH_2$). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ=146.0, 132.8, 129.5, 128.9, 128.8, 128.1, 116.1, 115.8, 94.2, 84.6, 64.7, 64.3. UV (EtOH): λ_{max} (log ε)=254 (4.22), 245 (4.28), 210 (4.47). Anal. Calcd for $C_{16}H_{13}FO_2$: C, 75.0; H, 5.07. Found: C, 74.89; H, 4.86.

1.2.9. 2-[3-Hydroxy-3-(*p*-chloro phenyl)]-prop-1-ynyl benzyl alcohol 23. White solid ($CHCl_3$+light petroleum ether), mp 105°C. IR (KBr): ν=3280, 3097, 1593, 1483, 1454, 1407 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ=7.26–7.54 (m, 8H, Ar–H), 5.68 (s, 1H, CHOH), 4.79 (s, 2H, $-CH_2$). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ=146.2, 132.8, 129.6, 129.2, 128.4, 128.1, 128.0, 116.2, 115.8, 94.2, 83.5, 64.7, 64.3. UV (EtOH): λ_{max} (log ε)=255 (4.28), 245 (4.34), 224 (4.19), 211 (4.48). Anal. Calcd for $C_{16}H_{13}ClO_2$: C, 70.45; H, 4.77. Found: C, 70.62; H, 4.74.

1.2.10. 2-[3-Hydroxy-3-(3,4-methylenedioxy) phenyl]-prop-1-ynyl benzyl alcohol 24. Yellowish solid ($CHCl_3$), mp 83°C. IR (KBr): ν=3265, 3136, 1504, 1488, 1438, 1402, 1357 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=6.71–7.39 (m, 8H, Ar–H), 5.87 (s, 2H, O–CH_2–O), 5.47 (s, 1H, CHOH), 4.67 (s, 2H, $-CH_2$). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ= 148.2, 147.9, 142.7, 134.1, 132.7, 129.2, 128.2, 127.9, 121.5, 120.8, 108.5, 107.9, 101.6, 94.1, 84.3, 64.9, 63.8. Anal. Calcd for $C_{17}H_{14}O_4$: C, 72.34; H, 4.96. Found: C, 72.72; H, 5.02.

1.3. Preparation of 3-alkylidene isobenzofuran-1(3*H*)-ones 25–34

General procedure: To a solution of the disubstituted alkynes **15**–**24** (200 mg) in acetone (10 mL), a solution of CrO_3 in water and concentrated H_2SO_4 (5 mL) was slowly added at 0°C under N_2 atmosphere and stirred for 2–3 h. Then the mixture was diluted with chilled water and the product was extracted with ether. The combined extracts were washed with saturated $NaHCO_3$ solution and distilled water, dried over anhydrous Na_2SO_4. Evaporation of the ether layer yielded yellow solid which was purified by chromatography on silica gel (60–120 mesh) using 80% $CHCl_3$ in petroleum ether (60–80°C) as the eluent. The material was further purified by crystallisation from a mixture of $CHCl_3$ and light petroleum ether.

1.3.1. (*E*)-3-(2′-Oxo-2′-phenyl)ethylidene isobenzofuran-1(3*H*)-one 25. White solid ($CHCl_3$+light petroleum ether), mp 134°C, (lit. 118–119°C).[26] IR (KBr): ν=1786, 1670, 1612, 1469, 1448 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ= 8.96 (d, 1H, *J*=9 Hz, Ar–C4–H), 7.43–8.08 (m, 8H, Ar–H), 7.13 (s, 1H, =CH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ= 189.8, 166.3, 158.3, 138.7, 136.7, 135.8, 133.8, 130.1, 129.3, 129.0, 128.9, 128.7, 128.2, 127.1, 125.8, 106.6. UV ($CHCl_3$): λ_{max} (log ε)=324 (3.87), 299 (3.89), 287 (3.92), 246 (4.04). Anal. Calcd for $C_{16}H_{10}O_3$:C, 76.80; H, 4.00. Found: C, 76.98; H, 4.02.

1.3.2. (*E*)-3-(2′-*o*-Methylphenyl-2′-oxo)ethylidene isobenzofuran-1(3*H*)-one 26. White small needles ($CHCl_3$+light petroleum ether), mp 102°C. IR (KBr): ν= 1799, 1670, 1616, 1585, 1471 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=9.03 (d, 1H, *J*=9 Hz, Ar–C4–H), 7.26–8.01 (m, 7H, Ar–H), 6.94 (s, 1H, =CH), 2.58 (s, 3H, $-CH_3$). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=193.7, 166.3, 157.6, 139.5, 138.4, 136.7, 135.8, 135.4, 133.3, 132.3, 132.1, 129.2, 128.0, 127.1, 126.3, 110.0, 21.3. UV (EtOH): λ_{max} (log ε)=325 (4.12), 300 (4.11), 290 (4.08), 249 (3.92). Anal. Calcd for $C_{17}H_{12}O_3$: C, 77.27; H, 4.54. Found: C, 76.94; H, 4.32.

1.3.3. (*E*)-3-(2′-*m*-Methylphenyl-2′-oxo)ethylidene isobenzofuran-1(3*H*)-one 27. Yellowish gum. IR (KBr): ν=1791, 1662, 1600, 1583, 1471,1456 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=9.03 (d, 1H, *J*=9 Hz, Ar–C4–H), 7.26–8.01 (m, 7H, Ar–H), 7.21 (s, 1H, =CH), 2.46 (s, 3H, $-CH_3$). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=190.1, 139.1, 136.7, 135.8, 134.6, 133.2, 129.3, 129.1, 128.1, 126.0, 125.8, 106.9, 21.8. Anal. Calcd for $C_{19}H_{12}O_3$: C, 77.27; H, 4.54. Found: C, 76.98; H, 4.26.

1.3.4. (*E*)-3-(2′-*p*-Methylphenyl-2′-oxo)ethylidene isobenzofuran-1(3*H*)-one 28. Light yellow crystalline solid ($CHCl_3$+light petroleum ether), mp 138°C, IR (KBr): ν=1786, 1662, 1614, 1598, 1583, 1471 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=9.01 (d, 1H, *J*=9 Hz, Ar–C4–H), 7.29–7.98 (m, 7H, Ar–H), 7.18 (s, 1H, =CH), 2.43 (s, 3H, $-CH_3$).^{13}C NMR (75.5 MHz, $CDCl_3$): δ=189.3, 166.3, 157.9, 144.8, 136.7, 136.2, 135.7, 133.1, 129.9, 128.9, 128.7, 128.1, 127.1, 125.7, 106.8, 22.1. UV (EtOH): λ_{max} (log ε)=329 (4.07), 301 (4.01), 287 (4.02), 266 (4.05), 243 (3.95). Anal. Calcd for $C_{17}H_{12}O_3$: C, 77.27; H, 4.54. Found: C, 77.35; H, 4.83.

1.3.5. (*E*)-3-(2′-*o*-Methoxyphenyl-2′-oxo)ethylidene isobenzofuran-1(3*H*)-one 29. Light yellow small needles ($CHCl_3$+light petroleum ether), mp 125°C. IR (KBr): ν=1792, 1655, 1600, 1470 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ=9.04 (d, 1H, *J*=9 Hz, Ar–C4–H), 7.41–7.90 (m, 7H, Ar–H), 7.15 (s, 1H, =CH), 3.80 (s, 3H, $-OCH_3$). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ=190.5, 165.8, 158.6,

156.4, 136.6, 135.9, 134.4, 133.6, 132.6, 130.6, 127.6, 126.0, 125.3, 120.9, 111.6, 111.5, 55.8. Anal. Calcd for $C_{17}H_{12}O_4$: C, 72.85; H, 4.28. Found: C, 72.53; H, 4.45.

1.3.6. (*E*)-3-(2′-*m*-Methoxyphenyl-2′-oxo)ethylidene isobenzofuran-1(3*H*)-one 30. Light yellow needles ($CHCl_3$+ light petroleum ether), mp 141°C. IR (KBr): ν=1796, 1668, 1618, 1595, 1585, 1487, 1471 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=9.04 (d, 1H, J=9 Hz, Ar–C4–H), 7.27–8.00 (m, 7H, Ar–H), 7.18, (s, 1H, =CH), 3.90 (s, 3H, $-OCH_3$). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=189.6, 166.2, 160.4, 158.3, 140.1, 135.8, 133.3, 130.4, 128.1, 126.2, 125.8, 122.5, 121.4, 120.5, 112.8, 106.7, 55.9. UV (EtOH): λ_{max} (log ε)=320 (4.06), 301 (4.07), 292 (4.04), 252 (3.92). Anal. Calcd for $C_{17}H_{12}O_4$: C, 72.85; H, 4.28. Found: C, 73.10; H, 4.66.

1.3.7. (*E*)-3-(2′-*p*-Methoxyphenyl-2′-oxo)ethylidene isobenzofuran-1(3*H*)-one 31. Colourless small needles ($CHCl_3$+light petroleum ether), mp 165°C, (lit. 163°C)[27] IR (KBr): ν=1793, 1656, 1596, 1568, 1510, 1456 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=8.99 (d, 1H, J=9 Hz, Ar–C4–H), 7.26–8.13 (m, 7H, Ar–H), 7.18 (s, 1H, =CH), 3.89 (s, 3H, $-OCH_3$). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=174.9, 165.6, 164.2, 157.6, 135.7, 133.1, 132.6, 131.7, 131.2, 129.8, 128.1, 127.1, 125.7, 114.6, 106.9, 56.1, 55.9. Anal. Calcd for $C_{17}H_{12}O_4$: C, 77.26; H, 4.57. Found: C, 77.30; H, 4.73.

1.3.8. (*E*)-3-(2′-*p*-Fluorophenyl-2′-oxo)ethylidene isobenzofuran-1(3*H*)-one 32. Light yellow solid ($CHCl_3$+ light petroleum ether), mp 155°C, (lit. 155–157°C)[23a] IR (KBr): ν=1795, 1674, 1625, 1593, 1504, 1473 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=9.02 (d, 1H, J=9 Hz, Ar–C4–H), 7.17–8.10 (m, 7H, Ar–H), 7.16 (s, 1H, =CH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=188.2, 168.0, 164.6, 158.5, 136.6, 135.8, 133.3, 131.5, 131.4, 130.7, 128.2, 127.1, 125.9, 116.5, 116.0, 106.2. UV (EtOH): λ_{max} (log ε)=327 (4.20), 303 (4.19), 250 (3.91). Anal. Calcd for $C_{16}H_9FO_3$: C, 71.64; H, 3.35. Found: C, 71.63; H, 3.25.

1.3.9. (*E*)-3-(2′-*p*-Chlorophenyl-2′-oxo)ethylidene isobenzofuran-1(3*H*)-one 33. Light yellow solid ($CHCl_3$+ light petroleum ether), mp 161°C, (lit. 165–167°C)[27] IR (KBr): ν=1799, 1670, 1614, 1585, 1471 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=9.03 (d, 1H, J=9 Hz, Ar–C4–H), 7.27–8.00 (m, 7H, Ar–H), 7.15 (s, 1H, =CH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=188.5, 166.1, 158.7, 140.3, 137.1, 136.5, 135.8, 133.4, 130.4, 130.1, 129.5, 129.3, 128.2, 127.1, 125.9, 106.1. UV (EtOH): λ_{max} (log ε)=330 (4.28), 305 (4.24), 249 (3.96). Anal. Calcd for $C_{16}H_9ClO_3$: C, 64.49; H, 3.16. Found: C, 64.24; H, 2.95.

1.3.10. (*E*)-3-[2′-(3,4-Methylenedioxy)phenyl-2′-oxo]-ethylidene isobenzofuran-1(3*H*)-one 34. Light yellow small needles ($CHCl_3$+light petroleum ether), mp 171°C. IR (KBr): ν=1790, 1660, 1620 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=8.89 (d, 1H, J=9 Hz, Ar–C4–H), 7.45–7.90 (m, 6H, Ar–H), 7.05 (s, 1H, =CH), 6.00 (s, 2H, O–CH_2–O) ^{13}C NMR (75.5 MHz, $CDCl_3$) δ=187.4, 165.9, 157.4, 152.2, 136.3, 135.3, 133.3, 132.7, 127.6, 126.8, 125.4, 125.0, 108.1, 106.4, 102.1. Anal. Calcd for $C_{17}H_{10}O_5$: C, 69.38, H, 3.42. Found: C, 69.05; H, 3.62.

1.4. Preparation of (*Z*)-3-(2′-aryl-2′-oxo)ethylidene isobenzofuran-1(3*H*)-ones 35–38 from the corresponding (*E*)-isomer 25, 28, 32, 33 through isomerisation. A typical procedure

1.4.1. (*Z*)-3-(2′-Oxo-2′-phenyl)ethylidene isobenzofuran-1(3*H*)-one 35. The (*E*)-isobenzofuranone **22** (100 mg) was dissolved in 96% sulphuric acid (2 mL) and stirred at room temperature for 2.5 h. Crushed ice was added to the mixture and it was filtered. The residue was washed with water (3×10 mL), saturated solution of $NaHCO_3$ (2×10 mL) and then water (2×10 mL). The product was crystallised from $CHCl_3$+light petroleum ether) to afford colourless small needles, mp 162°C (lit. 168°C),[26] (lit. 163–164°C).[13] IR (KBr): ν=1776, 1674, 1641, 1593, 1469 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=7.27–8.02 (m, 9H, Ar–H), 6.79 (s, 1H, =CH). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ=188.9, 153.5, 139.6, 138.5, 135.4, 134.8, 134.5, 133.6, 132.8, 130.9, 129.0, 126.5, 125.9, 125.3, 125.0, 121.6, 100.5. UV ($CHCl_3$): λ_{max} (log ε)=321 (4.14), 299 (4.17), 288 (4.15), 248 (4.06).

1.4.2. (*Z*)-3-(2′-*p*-Methylphenyl-2′-oxo)ethylidene isobenzofuran-1(3*H*)-one 36. Yellow crystalline solid ($CHCl_3$+petroleum ether); mp 208°C, (lit. 205°C)[27] IR (KBr): ν=1782, 1668, 1616, 1473 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=7.26–8.00 (m, 8H, Ar–H), 6.75 (s, 1H, =CH), 2.44 (s, 3H, $-CH_3$). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=188.5, 153.0, 144.6, 139.7, 136.0, 135.3, 132.6, 129.7, 129.2, 128.6, 126.4, 125.3, 121.5, 100.8, 22.1. Anal. Calcd for $C_{17}H_{12}O_3$; C, 77.27; H, 4.54. Found: C, 76.93; H, 4.24.

1.4.3. (*Z*)-3-(2′-*p*-Fluorophenyl-2′-oxo)ethylidene isobenzofuran-1(3*H*)-one 37. Light yellow crystals ($CHCl_3$+ light petroleum ether), mp 183°C. IR (KBr): ν=1782, 1674, 1624, 1587, 1508, 1473 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=7.13–8.06 (m, 8H, Ar–H), 6.73 (s, 1H, =CH). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ=187.4, 167.9, 166.1, 164.5, 153.5, 139.5, 135.5, 134.9, 132.8, 131.7, 131.6, 126.5, 121.6, 116.3, 116.0, 100.3. Anal. Calcd for $C_{16}H_9FO_3$: C, 71.64; H, 3.35. Found: C, 71.28; H, 3.02.

1.4.4. (*Z*)-3-(2′-*p*-Chlorophenyl-2′-oxo)ethylidene isobenzofuran-1(3*H*)-one 38. Yellowish small needles ($CHCl_3$+light petroleum), mp 200°C, (lit. 202–203°C)[27] IR (KBr): ν=1780, 1660, 1610, 1460 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=7.27–8.02 (m, 8H, Ar–H), 6.70 (s, 1H, =CH).^{13}C NMR (75.5 MHz, $CDCl_3$): δ=187.8, 140.2, 140.1, 136.8, 135.5, 132.9, 130.4, 129.4, 126.6, 125.3, 121.7, 100.2. Anal. Calcd for $C_{16}H_9ClO_3$: C, 64.49; H, 3.16. Found: C, 64.29; H, 2.98.

Acknowledgements

Grateful acknowledgement is made of the award of a Senior Research Fellowship to R. M. by the Council of Scientific and Industrial Research, New Delhi, India.

References

1. Bird, W. C., Cheeseman, G. W. H., Eds.; *Comprehensive Heterocyclic Chemistry*, Pergamon: Oxford, 1984; Vol. 4.
2. Rodrigo, R. *Tetrahedron* **1988**, *44*, 2093–2135.
3. Rickborn, B. *Advances in Theoretically Interesting Molecules*; Thummel, R. P., Ed.; JAI: Greenwich, Connecticut, 1989; Vol. 1.
4. Curtis, P. J.; Grove, J. F. *Nature (London)* **1947**, *160*, 574–575. Grove, J. F.; Hitchcock, P. B. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1145–1146.
5. Parisot, D.; Devys, D. M.; Ferezou, J. P.; Barbier, M. *Phytochemistry* **1983**, *22*, 1301.
6. Noguchi, T.; Fujita, S.; Kawanami, M. *J. Pharm. Soc. Jpn* **1937**, *57*, 196 (*Chem. Abstr.* **1938**, *32*, 3360). Gold, H. J.; Wilson III, C. W. *J. Org. Chem.* **1963**, *28*, 985–987. Pushan, W.; Xuanliang, G.; Yixiong, W.; Fukuyama, Y.; Miura, I.; Sugawara, M. *Phytochemistry* **1984**, *23*, 2033–2038. Van Wassenhove, F.; Dirinck, P.; Vulsteke, G.; Schamp, N. *Hort. Sci.* **1990**, *25*, 556.
7. Traxler, P.; Gruner, J.; Auden, J. A. L. *J. Antibiot.* **1977**, *30*, 289–296.
8. Rommele, G.; Traxler, P.; Wehrli, W. *J. Antibiot.* **1983**, *36*, 1539–1542.
9. Van Middlesworth, F.; Omstead, M. N.; Schmatz, D.; Bartizal, R.; Fromtling, R.; Bills, G.; Nollstadt, K.; Honeycutt, S.; Zweernik, M.; Garrity, G.; Wilson, K. *J. Antibiot.* **1991**, *44*, 45–51.
10. Kaneto, R.; Chiba, H.; Agematu, H.; Shibamoto, N.; Yoshioka, T.; Nishida, H.; Okamoto, R. *J. Antibiot.* **1993**, *46*, 247–251.
11. Barton, D. H. R.; de Varies, J. X. *J. Chem. Soc.* **1963**, 1916–1919. Yu, S.; You, S.; Chen, H. *Yaoxue Xuebao* **1984**, *19*, 486–490. Cheng, K. W.; Ching, L. L.; Hwa, L. S.; Yeh, H. P.; Yu, H. C.; Yang, W. G.; Wu, C. C. *Taiwan Yao Hsueh Tsa Chih* **1983**, *35*, 155–161 (*Chem. Abstr.* **1984**, *101*, 48511y). Fuska, J.; Fuskova, A.; Proksa, *B. Zb. Pr. Chemickotechnol. Fak. SVST* **1979–1981** (Pub. **1986**), 285–291; (*Chem. Abstr.* **1987**, *106*, 95582K). Lacova, M. Czech. Pat. 257,137, 1986; (*Chem. Abstr.* **1989**, *111*, 115015m) Boulet, C. A.; Poulton, G. A. *Heterocycles (Special Issue)* **1989**, *28*, 405–410.
12. Gabriel, S. *Ber. Dtsch. Chem. Ges.* **1886**, *19*, 838. Gabriel, S. *Ber. Dtsch. Chem. Ges.* **1893**, *26*, 952. Shriner, R. L.; Keyser, L. S. *J. Org. Chem.* **1940**, *5*, 200–203. Shapiro, S. L.; Geiger, K.; Freedman, L. *J. Org. Chem.* **1960**, *25*, 1860–1865. Zimmer, H.; Barry, R. D. *J. Org. Chem.* **1962**, *27*, 3710–3711. Napolitano, E.; Spinelli, G.; Fiaschi, R.; Marsili, A. *Synthesis* **1985**, 38–40. Howe, R. W. *J. Org. Chem.* **1973**, *38*, 4164–4167.
13. Kundu, N. G.; Pal, M.; Nandi, B. *J. Chem. Soc., Perkin Trans. 1* **1998**, 561–568 and references cited therein.
14. (a) Kundu, N. G.; Pal, M.; Mahanty, J. S.; Dasgupta, S. K. *J. Chem. Soc., Chem. Commun.* **1992**, 41–42. (b) Kundu, N. G.; Pal, M.; Mahanty, J. S.; De, M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2815–2820.
15. (a) Kundu, N. G.; Pal, M.; Mahanty, J. S.; Das, P.; Das, B. *Tetrahedron Lett.* **1993**, *34*, 1625–1628. (b) Mahanty, J. S.; De, M.; Das, P.; Kundu, N. G. *Tetrahedron* **1997**, *53*, 13397–13418.
16. (a) Chowdhury, C.; Kundu, N. G. *J. Chem. Soc., Chem. Commun.* **1996**, 1067–1068. (b) Chowdhury, C.; Chaudhuri, G.; Guha, S.; Mukherjee, A. K.; Kundu, N. G. *J. Org. Chem.* **1998**, *63*, 1863–1871.
17. (a) Chaudhuri, G.; Chowdhury, C.; Kundu, N. G. *Synlett* **1998**, 1273–1275. (b) Kundu, N. G.; Chaudhuri, G.; Upadhayay, A. *J. Org. Chem.* **2000**, *66*, 20–29.
18. (a) Kundu, N. G.; Khan, M. W. *Tetrahedron Lett.* **1997**, *38*, 6937–6940. (b) Khan, M. W.; Kundu, N. G. *Synlett* **1997**, 1435–1437. (c) Kundu, N. G.; Khan, M. W.; Mahanty, J. S. *J. Chem. Res. (S)* **1999**, 460–461. (d) Kundu, N. G.; Khan, M. W.; Mahanty, J. S. J. *Chem. Res. (M)* **1999**, 1901–1918. (e) Kundu, N. G.; Khan, M. W.; Mukhopadhyay, R. *Tetrahedron* **1999**, *55*, 12361–12376. (f) Kundu, N. G.; Khan, M. W. *Tetrahedron* **2000**, *56*, 4777–4792.
19. De, M.; Majumdar, D. P.; Kundu, N. G. *J. Indian Chem. Soc.* **1999**, *76*, 665–674.
20. Chaudhuri, G.; Kundu, N. G. *J. Chem. Soc., Perkin Trans. 1* **2000**, 775–779.
21. Nandi, B.; Kundu, N. G. *Org. Lett.* **2000**, *2*, 235–238.
22. (a) Cassar, L. *J. Organomet. Chem.* **1975**, *93*, 253–257. (b) Dieck, H. A.; Heck, R. F. *J. Organomet. Chem.* **1975**, *93*, 259–263. (c) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467–4470. (d) Torii, S.; Xu, L. H.; Okumoto, H. *Synlett* **1992**, 515–516. (e) Lu, X.; Huang, X.; Ma, S. *Tetrahedron Lett.* **1993**, *34*, 5963–5966. (f) Pal, M.; Kundu, N. G. *J. Chem. Soc., Perkin Trans. 1* **1996**, 449–451.
23. (a) Khan, M. W.; Kundu, N. G. *Synlett* **1999**, 456–458. (b) Previously Khan and Kundu (*Synlett* **1999**, 456–458) reported the formation of isobenzofurans from the reaction of *o*-iodobenzylalcohol with acetylenic carbinols in the presence of bis(triphenyl phosphine)palladium(II) chloride and cuprous iodide. On re-examination of the reaction, we (Mukhopadhyay and Kundu) however could isolate the disubstituted alkynes as the major products along with very small amount of the corresponding isobenzofurans in a few cases only under the reaction conditions. We therefore retract the earlier observation of Khan and Kundu on the exclusive formation of isobenzofurans as intermediates under the reaction conditions.
24. Chopard, P. A.; Hudson, R. F.; Searle, R. J. G. *Tetrahedron Lett.* **1965**, 2357–2360.
25. Elvidge, J. A.; Jones, D. E. H. *J. Chem. Soc. C* **1971**, 2424–2427.
26. Ingham, C. F.; Massy-Westropp, R. A.; Reynolds, G. D.; Thorpe, W. D. *Aust. J. Chem.* **1975**, *28*, 2499–2510.
27. Hori, K.; Takaishi, N. *Bull. Chem. Soc. Jpn* **1988**, *61*, 1791–1792.
28. Jones, E. R. H.; McCombie, J. T. *J. Chem. Soc.* **1942**, 733–735. Campbell, K. N.; Campbell, B. K.; Eby, L. T. *J. Am. Chem. Soc.* **1938**, *60*, 2882–2884.