# Copper(I) Iodide: A Catalyst for the Improved Synthesis of Aryl Propargyl Ethers

David Bell, Mark R. Davies, Graham R. Geen, Inderjit S. Mann*
SmithKline Beecham Pharmaceuticals, New Frontiers Science Park, Third Avenue, Harlow, Essex, CM19 5AW, England
Fax + 44(1279)622348
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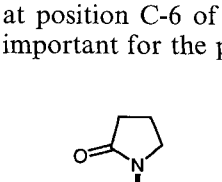
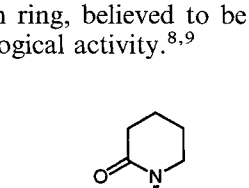
Copper(I) iodide catalyses the reaction between phenols and dialkylpropargyl chlorides to give aryl 1,1-dialkylpropargyl ethers **5a–k** and **7a–e** in good yields and purity. These ethers are important as precursors to the 2*H*-1-benzopyrans **8a–l** and **9a–e**.

There are many examples of biologically active compounds based on the benzopyran nucleus. Two of recent interest to us are the anti-hypertensive levcromakalim[1] **(1)**, and BRL 55834[2] **(2)**, an airways selective potassium channel activator for the treatment of asthma. Other potassium channel activators based on the benzopyran nucleus to have appeared recently are EMD 52692,[3] SDZ PCO-400,[4] Ro 31-6930,[5] WAY 120491[6] and EMD 57283.[7] A feature common to all these compounds is the presence of a strongly electron-withdrawing substituent at position C-6 of the benzopyran ring, believed to be important for the presence of biological activity.[8,9]



levcromakalim
**1**



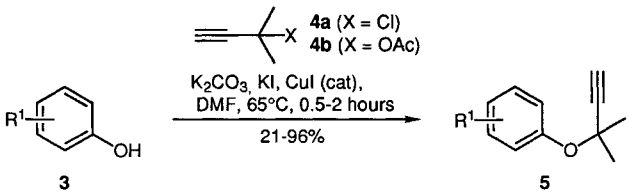
BRL 55834
**2**

The syntheses of levcromakalim and BRL 55834 require efficient and high yielding preparations of their benzopyran precursors, 6-cyano-2,2-dimethyl-2*H*-1-benzopyran[8,10,11] **(8a)** and 2,2-dimethyl-6-pentafluoroethyl-2*H*-1-benzopyran[2] **(8c)**. Current preparations of 2*H*-1-benzopyrans having electron-withdrawing substituents generally give low to moderate yields of product[8,11–13] and this prompted us to investigate improved procedures towards these compounds.

Many syntheses of 2*H*-1-benzopyrans are to be found in the literature.[14] Condensations of phenols with α,β-unsaturated aldehydes[15] or their acetal equivalents[16] are generally only suitable for polyhydric phenols or monohydric phenols with electron-donating substituents. Other methods such as reactions of salicaldehydes with acrylate esters[17,18] or vinyl[19] and allyl triphenylphosphonium salts[20] are generally low yielding, especially for 2,2-dimethyl-2*H*-1-benzopyrans, and suffer from lack of availability of the salicaldehyde starting materials.

Of the methods available, synthesis of 2*H*-1-benzopyrans via Claisen rearrangement of propargyl ethers is well documented,[21–23] and this approach was found to be the most suitable for our purposes. Aryl propargyl ethers are usually prepared by the reaction of phenols with a propargyl chloride in the presence of potassium carbonate and potassium iodide in acetone or DMF as solvent,[22,23] although other base/solvent combinations[8] and other methods[24] have also been used. However, the syntheses of aryl propargyl ethers from phenols having electron-withdrawing groups often give low yields by this method.[8] We have now found that the addition of a catalytic amount of copper(I) iodide to the reaction provides ethers in high yield and purity, and that this new method is especially useful when reacting phenols having electron-withdrawing groups. They can then be cyclised in a suitable high boiling solvent such as *N,N*-diethylaniline,[21] *o*-dichlorobenzene,[8,25] or DMF[23] to the corresponding 2*H*-1-benzopyrans.

For the preparation of BRL 55834 we required 2,2-dimethyl-6-pentafluoroethyl-2*H*-1-benzopyran **(8c)**, and the most efficient way of making this is to prepare 6-bromo[13,17] or 6-iodo-2*H*-1-benzopyran[26] **(8e, 8f)**, and convert it to **8c** using known methodology.[2] Thus the reaction of 4-bromophenol with 3-chloro-3-methylbut-1-yne[27] **(4a)** in the presence of potassium carbonate and potassium iodide in DMF or *N*-methylpyrrolidin-2-one gave only a 35% yield of pure ether **5e**, after a 24–48 hour reaction time (Table 1). It was then discovered that the addition of catalytic quantities of copper(I) iodide (2 mol%) resulted in a much faster reaction, and gave a 74% distilled yield of ether **5e** of high purity after a reaction time of only 2 hours. Significantly, the use of greater than 5 mol% of catalyst was found to be detrimental to the reaction, resulting in lower yields of product. The reaction with 4-iodophenol was found to proceed well without copper(I) iodide giving a high yield of **5f** after 24 hours, but in the presence of the catalyst a much faster reaction was nevertheless obtained, and the reaction was complete within 2 hours. The 2*H*-1-benzopyrans **8e** and **8f** resulting from cyclisation of the corresponding ethers could then be converted to **8c** in good yield. Alternatively, we also prepared 4-pentafluoroethylphenol[28] **(3c)** and reacted this using the new method to obtain the product **5c** directly in high yield (Scheme 1).



**3** **5**

**Scheme 1**

With the benefit of adding catalytic quantities of copper(I) iodide resulting in faster reaction rates and improved yields, we have evaluated a number of other phenols in this reaction (Table 1). The advantages of using copper(I) iodide are most pronounced in reactions involving

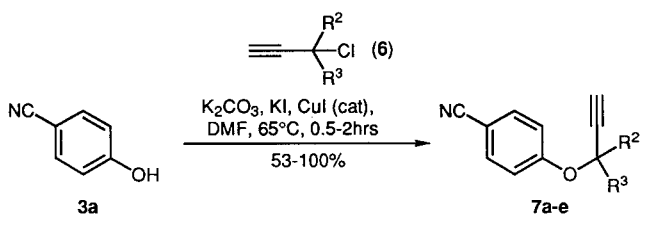
**Table 1.** Preparation of Aryl 1,1-Dimethylpropargyl Ethers **5a–k**

| Substrate | Product | $R^1$ | Yield (%) Without CuI | Yield (%) With CuI | mp (°C) or bp (°C/mbar) | Lit. mp (°C) or bp (°C/mmHg) |
|---|---|---|---|---|---|---|
| **3a** | **5a** | 4-CN | 32 | 96 | 29.5–31[a] | 29–30.5[25] |
| **3b** | **5b** | 4-$NO_2$ | 40 | 89 | 31–32.5[a] | 88–90/0.05[25] |
| **3c** | **5c** | 4-$C_2F_5$ | | 72 | 42–44/0.35 | |
| **3d** | **5d** | 4-Ac | 55 | 85 | 93–95/0.35 | 120/1[29] |
| **3e** | **5e**[b] | 4-Br | 35 | 74 | 68–70/0.35 | 96–106/1[30] |
| **3f** | **5f** | 4-I | 76 | 73 | 82–84/0.35 | |
| **3g** | **5g** | 4-Et | | 21 | 59–60/0.35 | |
| **3h** | **5h** | 4-OMe | 13 | 26 | 63–66/0.35 | 74–75/0.35[22] |
| **3i** | **5i** | 4-H | | 40 | 36–37/0.35 | 49–50/1[22] |
| **3j** | **5j** | 3-CN | | 84 | 78–80/0.35 | 97–98/0.2[8] |
| **3k** | **5k** | 2-CN | | 95 | 95–96/0.35 | 108–110/0.1[8] |

[a] Purified by distillation. Product crystallised on standing.
[b] *N*-Methylpyrrolidin-2-one used as solvent.

phenols having electron-withdrawing substituents, such as 4-cyanophenol **(3a)** and 4-nitrophenol **(3b)** which gave yields of ethers **5a** and **5b** of 96% and 89% respectively after reaction times of 1 hour. Both these examples give significantly higher yields than the previously published procedures (**5a** and **5b** were obtained in yields of 69%[8] and 45%[31] respectively after reaction times of 4 days). Phenols lacking electron-withdrawing substituents were found not to be as efficient at reacting under these conditions, although other methods are available for preparing these compounds.[22,23]

In order to examine further the scope of this reaction we were interested in preparing 2*H*-1-benzopyrans with different 2-alkyl substituents by this method. Thus a series of dialkyl propargyl chlorides[27] **(6a–e)** was prepared and their reactions with 4-cyanophenol were evaluated (Scheme 2). Although the yields were not as good as those obtained using 3-chloro-3-methylbut-1-yne **(4a)**, better yields were still obtained when copper(I) iodide was employed as a catalyst, even though in most cases unreacted phenol still remained. Even highly hindered substrates such as methyl-*tert*-butylpropargyl chloride **(6c)** and diisopropylpropargyl chloride **(6e)** gave reasonable yields of ethers (Table 2).




**Scheme 2**

During the course of preparation of this manuscript, another publication appeared detailing the preparation of aryl 1,1-dimethylpropargyl ethers catalysed by copper(I) chloride in acetonitrile containing 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).[32] Contrary to the findings in this paper we have found that the use of the acetate **4b**[33] (Scheme 1) also gives aryl 1,1-dimethylpropargyl ethers in high yield by our method. Thus reaction of **4b** with 4-cyanophenol under standard conditions afforded the corresponding ether **5a** in 84% yield after distillation.

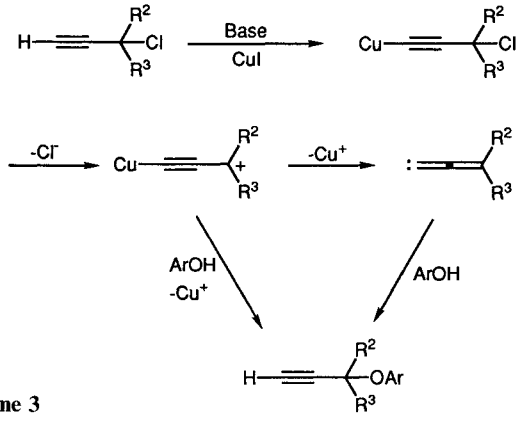
From a mechanistic viewpoint solvolysis of 3-chloro-3-methylbut-1-yne under basic conditions is believed to proceed via deprotonation of the terminal acetylenic proton, resulting in the formation of a zwitterionic and/or a carbenoid species, which then reacts with a nucleophile[34] (Scheme 3). A recent publication[35] has shown that Cu(I) salts also catalyse the amination of propargyl acetates and phosphates by the proposed intermediacy of a Cu acetylide species, and a similar mechanistic rationale could therefore be postulated for the reaction with phenols.

All propargyl ethers were cyclised to their corresponding 2*H*-1-benzopyrans (Table 3) in DMF containing *N,N*-diethylaniline at 140–150°C in moderate to high yields (Scheme 4).

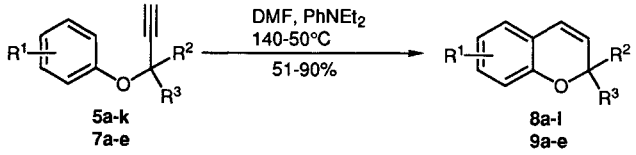
**Table 2.** Preparation of Aryl 1,1-Dialkylpropargyl Ethers **5a** and **7a–e**

| Chloride | Product | $R^2$ | $R^3$ | Without CuI Yield (%) | With CuI | mp (°C) or bp (°C/mbar) |
|---|---|---|---|---|---|---|
| **4a** | **5a** | Me | Me | 32 | 96 | 29.5–31 |
| **6a** | **7a**[30] | Me | Et | 16 | 100 | 86–88/0.35 |
| **6b** | **7b** | Et | Et | 18 | 91 | 97–100/0.35 |
| **6c** | **7c** | Me | *t*-Bu | 13 | 53 | 60–60.5[a] |
| **6d** | **7d** | $-(CH_2)_5-$ | | 18 | 85 | 52–53[b] |
| **6e** | **7e** | *i*-Pr | *i*-Pr | 26 | 62 | c |

[a] Recrystallised from hexane.
[b] Recrystallised from 10% EtOAc in hexane.
[c] Material cyclises to the 2*H*-1-benzopyran on attempted distillation.



Scheme 3



Scheme 4

We have demonstrated that for phenols having electron-withdrawing substituents that their reaction with dialkylpropargyl chlorides proceeds significantly faster in the presence of catalytic quantities of copper(I) iodide, resulting in much higher yields of aryl propargyl ethers.

$^1$H NMR spectra were recorded either on a Bruker AMX 400 spectrometer at 400 MHz, or on a Jeol GX 270 spectrometer at 270 MHz. Signals are quoted as $\delta$ppm downfield from internal tetramethylsilane. $^{13}$C NMR spectra were recorded on the same instruments at 100 MHz (Bruker), or 67.5 MHz (Jeol), chemical shifts were referenced to the deuterated solvent signals. Mass spectra were obtained on a Fisons VG Biotic Trio 2 spectrometer. HPLC analyses were using a Lichrosphere 60 RP-Select B 5 μm, 125 mm × 4 mm column eluting with solutions of acetonitrile/0.05 M potassium dihydrogen phosphate unbuffered; UV detection was employed at 235 nm. Melting points were obtained with a Mettler FP90 Thermosystem.

**3-(4-Cyanophenoxy)-3-methylbut-1-yne (5a); Typical Procedure:**
3-Chloro-3-methylbut-1-yne **(4a)** (4.1 g, 40 mmol) was added to a mixture of 4-cyanophenol **(3a)** (2.38 g, 20 mmol), 325 mesh $K_2CO_3$ (5.52 g, 40 mmol), KI (5.64 g, 34 mmol) and CuI (0.076 g, 0.4 mmol) in dry DMF (20 mL) under Ar, and the reaction stirred at 65 °C until no further conversion to product took place when monitoring the reaction by HPLC. On cooling, water (150 mL) was added and the mixture extracted with hexane (2 × 150 mL). The combined hexane extracts were washed successively with 2 N NaOH (150 mL), 2 N HCl (150 mL), and water (100 mL), before drying ($Na_2SO_4$) and removal of solvent afforded crude **5a** as an oil. Vacuum distillation gave a 96% yield of purified **5a**.

When using the acetate **4b**, the reaction was carried out at 75 °C for 6 h and gave an 84% yield of distilled **5a**.

**6-Cyano-2,2-dimethyl-2*H*-1-benzopyran (8a); Typical Procedure:**
A solution of the ether **5a** (1.85 g, 10 mmol) in dry DMF (10 mL) and *N*,*N*-diethylaniline (0.5 mL) was stirred under Ar at 140 °C overnight. On cooling, the reaction mixture was poured into water (100 mL) and the mixture extracted with hexane (1 × 100 mL, 2 × 50 mL). The combined extracts were washed successively with 2 N NaOH (2 × 50 mL), 2 N HCl (2 × 50 mL) and water (50 mL), before drying ($Na_2SO_4$) and removal of solvent to afford crude **8a** as a yellow oil (1.70 g, 92%). This was recrystallised from hexane to afford a 67% yield of pure **8a**.

**Table 3.** Cyclisation of Arylpropargyl Ethers **5a–k** and **7a–e** to 2*H*-1-Benzopyrans **8a–l** and **9a–e**

| Substrate | Product | $R^1$ | $R^2$ | $R^3$ | Yield (%) | mp (°C) or bp (°C/mbar) | Lit. mp (°C) or bp (°C/mmHg) |
|---|---|---|---|---|---|---|---|
| **5a** | **8a** | 6-CN | Me | Me | 67 | 48–49.5[a] | 36–37[25] |
| **5b** | **8b** | 6-$NO_2$ | Me | Me | 74 | 71.5–72.5[b] | 71–72[25] |
| **5c** | **8c** | 6-$C_2F_5$ | Me | Me | 84 | 55–57/0.35 | 62/0.3[2] |
| **5d** | **8d** | 6-Ac | Me | Me | 84 | 98–100/0.35 | 135–136/4[36] |
| **5e** | **8e** | 6-Br | Me | Me | 73 | 83–84/0.35 | 143–146/19[17] |
| **5f** | **8f** | 6-I | Me | Me | 83 | 91–93/0.35 | see ref. 26 |
| **5g** | **8g** | 6-Et | Me | Me | 70 | 63–65/0.35 | |
| **5h** | **8h** | 6-OMe | Me | Me | 69 | 71–73/0.35 | 132–136/15[22] |
| **5i** | **8i** | 6-H | Me | Me | 67 | 42–45/0.35 | 79–80/2.5[22] |
| **5j** | **8j** | 5-CN | Me | Me | 51[d] | 83–85/0.35 | 77–80/0.5[8] |
| **5j** | **8k** | 7-CN | Me | Me | 28[d] | 48–49[c] | see ref. 8 |
| **5k** | **8l** | 8-CN | Me | Me | 81 | 106–8/0.35 | 108–110/0.6[8] |
| **7a** | **9a** | 6-CN | Me | Et | 90 | 104–7/0.35 | |
| **7b** | **9b** | 6-CN | Et | Et | 88 | 108–12/0.35 | see ref. 37 |
| **7c** | **9c** | 6-CN | Me | *t*-Bu | 50 | 58.5[b] | |
| **7d** | **9d** | 6-CN | $-(CH_2)_5-$ | | 51 | 94.5–95.5[b] | 94–95[3] |
| **7e** | **9e** | 6-CN | *i*-Pr | *i*-Pr | 57 | 77–77.5[b] | |

[a] Purified by distillation, product solidified on standing.
[b] Recrystallised from hexane.
[c] Purified by chromatography.
[d] Obtained as a 51 : 28 mixture of 5-CN : 7-CN substituted products.

**Table 4.** $^1H$ and $^{13}C$ NMR Data for Aryl Propargyl Ethers **5a–k** and **7a–e**

| Product | $^1H$ NMR ($CDCl_3$) $\delta$ | $^{13}C$ NMR ($CDCl_3$) $\delta$, $J$ (Hz) |
|---|---|---|
| **5a** | 1.70 (s, 6H, 2 × $CH_3$), 2.65 (s, 1H, CCH), 7.28 (m, 2H, H-2,6), 7.57 (m, 2H, H-3,5) | 29.5 (2 × $CH_3$), 72.7 [$\underline{C}(CH_3)_2$], 75.2 ($C\underline{C}H$), 84.7 ($\underline{C}CH$), 105.2 (C-4), 119.1 (CN), 120.0 (C-2,6), 133.4 (C-3,5), 159.4 (C-1) |
| **5b** | 1.73 (s, 6H, 2 × $CH_3$), 2.68 (s, 1H, CCH), 7.30 (m, 2H, H-2,6), 8.18 (m, 2H, H-3,5) | 29.5 (2 × $CH_3$), 73.0 [$\underline{C}(CH_3)_2$], 75.5 ($C\underline{C}H$), 84.5 ($\underline{C}CH$), 119.0 (C-2,6), 125.2 (C-3,5), 142.2 (C-4), 161.3 (C-1) |
| **5c** | 1.69 (s, 6H, 2 × $CH_3$), 2.61 (s, 1H, CCH), 7.31 (m, 2H, H-2,6), 7.50 (m, 2H, H-3,5) | 29.6 (2 × $CH_3$), 72.5 [$\underline{C}(CH_3)_2$], 74.8 ($C\underline{C}H$), 85.3 ($\underline{C}CH$), 113.7 (tq, $J$ = 253, 38, $CF_2$), 119.3 (qt, $J$ = 286, 40, $CF_3$), 120.0 (C-2,6), 122.1 (t, $J$ = 24, C-4), 127.6 (t, $J$ = 6, C-3,5), 158.8 (C-1) |
| **5d** | 1.71 (s, 6H, 2 × $CH_3$), 2.58 (s, 3H, $CH_3CO$), 2.67 (s, 1H, CCH), 7.29 (m, 2H, H-2,6), 7.92 (m, 2H, H-3,5) | 26.4 ($\underline{C}H_3CO$), 29.6 (2 × $CH_3$), 72.4 [$\underline{C}(CH_3)_2$], 74.8 ($C\underline{C}H$), 85.2 ($\underline{C}CH$), 119.3 (C-2,6), 129.9 (C-3,5), 131.3 (C-4), 160.0 (C-1), 196.9 ($CH_3\underline{C}O$) |
| **5e** | 1.64 (s, 6H, 2 × $CH_3$), 2.58 (s, 1H, CCH), 7.09 (m, 2H, H-2,6), 7.38 (m, 2H, H-3,5) | 29.5 (2 × $CH_3$), 72.8 [$\underline{C}(CH_3)_2$], 74.3 ($C\underline{C}H$), 85.7 ($\underline{C}CH$), 115.7 (C-4), 123.3 (C-2,6), 131.9 (C-3,5), 154.7 (C-1) |
| **5f** | 1.63 (s, 6H, 2 × $CH_3$), 2.57 (s, 1H, CCH), 6.97 (m, 2H, H-2,6), 7.56 (m, 2H, H-3,5) | 29.5 (2 × $CH_3$), 72.6 [$\underline{C}(CH_3)_2$], 74.3 ($C\underline{C}H$), 85.6 ($\underline{C}CH$), 86.0 (C-4), 123.5 (C-2,6), 137.9 (C-3,5), 155.5 (C-1) |
| **5g** | 1.22 (t, 3H, $CH_2C\underline{H}_3$), 1.63 (s, 6H, 2 × $CH_3$), 2.53 (s, 1H, CCH), 2.60 (q, 2H, $C\underline{H}_2CH_3$), 7.10 (m, 4H, Ar) | 15.6 ($CH_2\underline{C}H_3$), 28.1 ($\underline{C}H_2CH_3$), 29.6 [$C(\underline{C}H_3)_2$], 72.4 [$\underline{C}(CH_3)_2$], 73.6 ($C\underline{C}H$), 86.4 ($\underline{C}CH$), 121.7 (C-2,6), 128.1 (C-3,5), 138.8 (C-4), 153.4 (C-1) |
| **5h** | 1.59 (s, 6H, 2 × $CH_3$), 2.51 (s, 1H, CCH), 3.77 (s, 3H, $OCH_3$), 6.80 (m, 2H, H-3,5), 7.12 (m, 2H, H-2,6) | 29.5 (2 × $CH_3$), 55.5 ($OCH_3$), 73.0 [$\underline{C}(CH_3)_2$], 73.6 ($C\underline{C}H$), 86.4 ($\underline{C}CH$), 113.9 (C-3,5), 123.7 (C-2,6), 148.9 (C-1), 155.8 (C-4) |
| **5i** | 1.63 (s, 6H, 2 × $CH_3$), 2.53 (s, 1H, CCH), 7.03 (m, 1H, H-4), 7.20 (m, 2H, H-2,6), 7.26 (m, 2H, H-3,5) | 29.6 (2 × $CH_3$), 72.3 [$\underline{C}(CH_3)_2$], 73.8 ($C\underline{C}H$), 86.2 ($\underline{C}CH$), 121.5 (C-2,6), 122.9 (C-4), 128.9 (C-3,5), 155.6 (C-1) |
| **5j** | 1.66 (s, 6H, 2 × $CH_3$), 2.64 (s, 1H, CCH), 7.34 (dd, 1H, H-4), 7.37 (t, 1H, H-5), 7.42 (dd, 1H, H-6), 7.51 (d, 1H, H-2) | 29.7 (2 × $CH_3$), 73.4 [$\underline{C}(CH_3)_2$], 75.4 ($C\underline{C}H$), 85.2 ($\underline{C}CH$), 113.0 (C-3), 118.9 (CN), 124.3 (C-2), 126.0 (C-4), 126.5 (C-6), 130.1 (C-5), 156.1 (C-1). |
| **5k** | 1.75 (s, 6H, 2 × $CH_3$), 2.66 (s, 1H, CCH), 7.08 (t, 1H, H-4), 7.50 (t, 1H, H-5), 7.56 (d, 1H, H-3), 7.65 (d, 1H, H-6) | 29.7 (2 × $CH_3$), 74.5 [$\underline{C}(CH_3)_2$], 75.5 ($C\underline{C}H$), 85.1 ($\underline{C}CH$), 106.4 (C-2), 117.0 (CN), 119.8 (C-6), 122.7 (C-4), 133.6 (C-3), 133.8 (C-5), 158.2 (C-1). |
| **7a** | 1.10 (t, 3H, $CH_2C\underline{H}_3$), 1.62 (s, 3H, $CH_3$), 1.95 (m, 2H, $C\underline{H}_2CH_3$), 2.67 (s, 1H, CCH), 7.28 (m, 2H, H-2,6), 7.56 (m, 2H, H-3,5) | 8.5 ($CH_2\underline{C}H_3$), 26.1 ($CH_3$), 35.4 ($\underline{C}H_2$), 76.3 ($C\underline{C}H$ and [$\underline{C}$(Et)(Me)]), 83.7 ($\underline{C}CH$), 105.0 (C-4), 119.1 (CN), 120.0 (C-2,6), 133.3 (C-3,5), 159.5 (C-1). |
| **7b** | 1.03 (t, 6H, 2 × $CH_3$), 1.95 (m, 4H, 2 × $CH_2$), 2.68 (s, 1H, CCH), 7.28 (m, 2H, H-2,6), 7.55 (m, 2H, H-3,5) | 8.2 (2 × $CH_3$), 31.3 (2 × $CH_2$), 77.4 ($C\underline{C}H$), 80.0 [$\underline{C}(Et)_2$], 83.1 ($\underline{C}CH$), 105.0 (C-4), 119.2 (CN), 120.1 (C-2,6), 133.4 (C-3,5), 159.7 (C-1) |
| **7c** | 1.16 (s, 9H, $C(CH_3)_3$), 1.54 (s, 3H, $CH_3$), 2.64 (s, 1H, CCH), 7.29 (m, 2H, H-2,6), 7.56 (m, 2H, H-3,5) | 20.8 ($CH_3$), 25.1 [$C(\underline{C}H_3)_3$], 39.6 [$\underline{C}(CH_3)_3$], 77.1 ($C\underline{C}H$), 82.0 [$\underline{C}$(Me)(*t*-Bu)], 83.5 ($\underline{C}CH$), 105.3 (C-4), 119.2 (CN), 120.9 (C-2,6), 133.3 (C-3,5), 159.9 (C-1). |
| **7d** | 1.4–2.1 (m, 10H, 5 × $CH_2$), 2.72 (s, 1H, CCH), 7.31 (m, 2H, H-2,6), 7.56 (m, 2H, H-3,5) | 22.4 (2 × $CH_2$), 25.0 ($CH_2$), 37.5 (2 × $CH_2$), 76.1 [$\underline{C}(CH_2)_2$], 77.0 ($C\underline{C}H$), 84.0 ($\underline{C}CH$), 105.0 (C-4), 119.2 (CN), 120.1 (C-2,6), 133.4 (C-3,5), 159.3 (C-1). |
| **7e** | 1.06 (d, 6H, 2 × $CH_3$), 1.11 (d, 6H, 2 × $CH_3$), 2.28 (spt, 2H, 2 × CH), 2.75 (s, 1H, CCH), 7.30 (m, 2H, H-2,6), 7.52 (m, 2H, H-3,5) | 17.8 (2 × $CH_3$), 18.6 (2 × $CH_3$), 36.0 (2 × CH), 80.9 ($\underline{C}CH$), 81.1 ($C\underline{C}H$), 88.5 [$C(i\text{-}Pr)_2$], 105.2 (C-4), 119.5 (CN), 121.8 (C-2,6), 133.2 (C-3,5), 161.7 (C-1). |

**Table 5.** $^1H$ and $^{13}C$ NMR Data for 2*H*-1-Benzopyrans **8a–l** and **9a–e**

| Product[a] | $^1H$ NMR ($CDCl_3$) $\delta$, $J$ (Hz) | $^{13}C$ NMR ($CDCl_3$) $\delta$, $J$ (Hz) |
|---|---|---|
| **8a** | 1.45 (s, 6H, 2 × $CH_3$), 5.70 (d, 1H, $J$ = 10.0, H-3), 6.28 (d, 1H, $J$ = 10.0, H-4), 6.79 (d, 1H, $J$ = 8.4, H-8), 7.24 (d, 1H, $J$ = 2.1, H-5), 7.37 (dd, 1H, $J$ = 2.1, 8.4, H-7) | 28.4 (2 × $CH_3$), 77.8 (C-2), 103.8 (C-6), 117.2 (C-8), 119.2 (CN), 120.6 (C-4), 121.7 (C-4a), 130.1 (C-5), 132.2 (C-3), 133.3 (C-7), 156.8 (C-8a) |
| **8b** | 1.48 (s, 6H, 2 × $CH_3$), 5.75 (d, 1H, $J$ = 10.0, H-3), 6.35 (d, 1H, $J$ = 10.0, H-4), 6.81 (d, 1H, $J$ = 8.9, H-8), 7.89 (d, 1H, $J$ = 2.8, H-5), 8.02 (dd, 1H, $J$ = 2.8, 8.9, H-7) | 28.5 (2 × $CH_3$), 78.5 (C-2), 116.5 (C-8), 120.8 (C-4, 4a), 122.0 (C-5), 125.2 (C-7), 132.3 (C-3), 141.4 (C-6), 158.7 (C-8a) |
| **8c** | 1.45 (s, 6H, 2 × $CH_3$), 5.67 (d, 1H, $J$ = 9.9, H-3), 6.32 (d, 1H, $J$ = 9.9, H-4), 6.83 (d, 1H, $J$ = 8.4, H-8), 7.17 (d, 1H, $J$ = 2.2, H-5), 7.30 (dd, 1H, $J$ = 2.2, 8.4, H-7) | 28.3 (2 × $CH_3$), 77.3 (C-2), 113.6 (tq, $J$ = 38, 253, $CF_2$), 116.6 (C-8), 119.3 (qt, $J$ = 40, 286, $CF_3$), 120.7 (t, $J$ = 24, C-6), 121.3 (C-4a), 121.4 (C-4), 124.6 (t, $J$ = 6.2, C-5), 127.4 (t, $J$ = 6.2, C-7), 131.8 (C-3), 156.0 (C-8a) |
| **8d** | 1.45 (s, 6H, 2 × $CH_3$), 2.52 (s, 3H, $COCH_3$), 5.66 (d, 1H, $J$ = 9.9, H-3), 6.34 (d, 1H, $J$ = 9.9, H-4), 6.78 (d, 1H, $J$ = 8.4, H-8), 7.61 (d, 1H, $J$ = 2.2, H-5), 7.74 (dd, 1H, $J$ = 2.2, 8.4, H-7) | 26.3 ($CH_3$), 28.4 (2 × $CH_3$), 77.5 (C-2), 116.1 (C-8), 120.7 (C-4a), 121.7 (C-4), 126.9 (C-5), 130.2 (C-7), 130.4 (C-6), 131.2 (C-3), 157.4 (C-8a), 196.7 (CO) |

**Table 5.** (continued)

| Product[a] | $^1$H NMR ($CDCl_3$) $\delta$, $J$ (Hz) | $^{13}$C NMR ($CDCl_3$) $\delta$, $J$ (Hz) |
|---|---|---|
| **8e** | 1.41 (s, 6H, 2 × $CH_3$), 5.62 (d, 1H, $J$ = 9.8, H-3), 6.23 (d, 1H, $J$ = 9.8, H-4), 6.64 (d, 1H, $J$ = 8.5, H-8), 7.07 (d, 1H, $J$ = 2.4, H-5), 7.17 (dd, 1H, $J$ = 2.4, 8.5, H-7) | 28.2 (2 × $CH_3$), 76.8 (C-2), 112.8 (C-6), 118.3 (C-8), 121.6 (C-4), 123.4 (C-4a), 129.0 (C-5), 131.8 (C-7), 132.2 (C-3), 152.3 (C-8a) |
| **8f** | 1.40 (s, 6H, 2 × $CH_3$), 5.60 (d, 1H, $J$ = 9.8, H-3), 6.21 (d, 1H, $J$ = 9.8, H-4), 6.53 (d, 1H, $J$ = 8.4, H-8), 7.25 (d, 1H, $J$ = 2.2, H-5), 7.35 (dd, 1H, $J$ = 2.2, 8.4, H-7) | 28.0 (2 × $CH_3$), 76.5 (C-2), 82.4 (C-6), 118.6 (C-8), 121.1 (C-4), 123.7 (C-4a), 131.7 (C-3), 134.6 (C-5), 137.6 (C-7), 152.8 (C-8a) |
| **8g** | 1.19 (t, 3H), 1.41 (s, 6H, 2 × $CH_3$), 2.54 (q, 2H, $CH_2$), 5.58 (d, 1H, $J$ = 9.7, H-3), 6.28 (d, 1H, $J$ = 9.7, H-4), 6.69 (d, 1H, $J$ = 8.2, H-8), 6.79 (d, 1H, $J$ = 2.1, H-5), 6.92 (dd, 1H, $J$ = 2.1, 8.2, H-7) | 16.0 ($CH_3$), 28.2 (2 × $CH_3$), 28.3 ($CH_2$), 76.2 (C-2), 116.3 (C-8), 121.3 (C-4a), 122.7 (C-4), 125.8 (C-5), 128.6 (C-7), 131.0 (C-3), 136.7 (C-6), 151.1 (C-8a) |
| **8h** | 1.40 (s, 6H, 2 × $CH_3$), 3.74 (s, 3H, $OCH_3$), 5.62 (d, 1H, $J$ = 9.8, H-3), 6.27 (d, 1H, $J$ = 9.8, H-4), 6.54 (d, 1H, $J$ = 2.8, H-5), 6.65 (dd, 1H, $J$ = 2.8, 8.7, H-7), 6.70 (d, 1H, $J$ = 8.7, H-8) | 27.9 (2 × $CH_3$), 56.0 ($OCH_3$), 76.0 (C-2), 111.8 (C-5), 114.5 (C-7), 117.1 (C-8), 122.2 (C-4a), 122.7 (C-4), 132.0 (C-3), 147.0 (C-8a), 154.0 (C-6) |
| **8i** | 1.42 (s, 6H, 2 × $CH_3$), 5.58 (d, 1H, $J$ = 9.8, H-3), 6.30 (d, 1H, $J$ = 9.8, H-4), 6.76 (d, 1H, $J$ = 7.8, H-8), 6.83 (dt, 1H, $J$ = 1.2, 7.5, H-6), 6.95 (dd, 1H, $J$ = 1.6, 7.4, H-5), 7.08 (dt, 1H, $J$ = 1.6, 7.8, H-7) | 28.0 (2 × $CH_3$), 76.1 (C-2), 116.3 (C-8), 120.7 (C-6), 121.3 (C-4a), 122.3 (C-4), 126.3 (C-5), 129.0 (C-7), 130.7 (C-3), 152.9 (C-8a) |
| **8j** | 1.45 (s, 6H, 2 × $CH_3$), 5.83 (d, 1H, $J$ = 10.0, H-3), 6.65 (d, 1H, $J$ = 10.0, H-4), 6.96 (dd, 1H, $J$ = 2.4, 8.0, H-8), 7.13 (m, 2H, H-6,7) | 27.9 (2 × $CH_3$), 77.0 (C-2), 108.9 (C-5), 117.2 (CN), 118.9 (C-4), 121.0 (C-8), 123.8 (C-4a), 124.6 (C-6), 129.2 (C-7), 134.2 (C-3), 153.2 (C-8a) |
| **8k** | 1.45 (s, 6H, 2 × $CH_3$), 5.77 (d, 1H, $J$ = 10.0, H-3), 6.32 (d, 1H, $J$ = 10.0, H-4), 7.00 (d, 1H, $J$ = 1.6, H-8), 7.01 (d, 1H, $J$ = 8.4, H-5), 7.11 (dd, 1H, $J$ = 1.6, 8.4, H-6) | 28.1 (2 × $CH_3$), 77.1 (C-2), 111.9 (C-7), 118.9 (CN), 119.6 (C-8), 121.2 (C-4), 124.7 (C-6), 125.6 (C-4a), 126.7 (C-5), 134.1 (C-3), 153.1 (C-8a) |
| **8l** | 1.50 (s, 6H, 2 × $CH_3$), 5.70 (d, 1H, $J$ = 10.0, H-3), 6.30 (d, 1H, $J$ = 10.0, H-4), 6.86 (t, 1H, $J$ = 7.9, H-6), 7.14 (dd, 1H, $J$ = 1.7, 7.5, H-5), 7.32 (dd, 1H, $J$ = 1.7, 7.9, H-7) | 28.3 (2 × $CH_3$), 78.6 (C-2), 100.5 (C-8), 116.3 (CN), 120.7 (C-6), 120.8 (C-4), 121.8 (C-4a), 130.3 (C-5), 132.1 (C-3,7), 155.7 (C-8a) |
| **9a** | 0.95 (t, 3H, $CH_2CH_3$), 1.40 (s, 3H, $CH_3$), 1.72 (m, 2H, $CH_2CH_3$), 5.63 (d, 1H, $J$ = 10.0, H-3), 6.33 (d, 1H, $J$ = 10.0, H-4), 6.78 (1H, d, $J$ = 8.3, H-8), 7.22 (d, 1H, $J$ = 2.1, H-5), 7.36 (dd, 1H, $J$ = 2.1, 8.3, H-7) | 8.1 ($CH_2CH_3$), 26.7 ($CH_3$), 34.5 ($CH_2$), 80.7 (C-2), 103.5 (C-6), 116.9 (C-8), 119.3 (CN), 121.4 (C-4), 121.6 (C-4a), 130.1 (C-5), 131.0 (C-3), 133.3 (C-7), 157.3 (C-8a) |
| **9b** | 0.93 (t, 6H, 2 × $CH_3$), 1.70 (m, 4H, 2 × $CH_2$), 5.54 (d, 1H, $J$ = 10.2, H-3), 6.39 (d, 1H, $J$ = 10.2, H-4), 6.77 (d, 1H, $J$ = 8.4, H-8), 7.20 (d, 1H, $J$ = 2.1, H-5), 7.34 (dd, 1H, $J$ = 2.1, 8.4, H-7) | 7.9 (2 × $CH_3$), 33.2 ($CH_2$), 83.9 (C-2), 103.2 (C-6), 116.4 (C-8), 119.3 (CN), 121.5 (C-4a), 122.4 (C-4), 129.5 (C-3), 130.1 (C-5), 133.4 (C-7), 158.1 (C-8a) |
| **9c** | 1.02 (s, 9H, 3 × $CH_3$), 1.37 (s, 3H, $CH_3$), 5.80 (d, 1H, $J$ = 10.4, H-3), 6.32 (d, 1H, $J$ = 10.4, H-4), 6.75 (d, 1H, $J$ = 8.4, H-8), 7.19 (d, 1H, $J$ = 2.0, H-5),. 7.35 (dd, 1H, $J$ = 2.0, 8.4, H-7) | 22.7 ($CH_3$), 24.9 [$C(CH_3)_3$], 39.2 [$C(CH_3)_3$], 85.2 (C-2), 103.1 (C-6), 116.5 (C-8), 119.4 (CN), 121.2 (C-4,4a), 129.0 (C-3), 130.0 (C-5), 133.4 (C-7), 157.7 (C-8a) |
| **9d** | 1.35 (m, 2H, $CH_2$), 1.56 (m, 4H, 2 × $CH_2$), 1.73 (m, 2H, $CH_2$), 1.92 (m, 2H, $CH_2$), 5.73 (d, 1H, $J$ = 10.0, H-3), 6.29 (d, 1H, $J$ = 10.0, H-4), 6.84 (d, 1H, $J$ = 8.4, H-8), 7.23 (d, 1H, $J$ = 2.0, H-5), 7.37 (dd, 1H, $J$ = 2.0, 8.4, H-7) | 21.1 (2 × $CH_2$), 25.1 ($CH_2$), 36.3 (2 × $CH_2$), 78.5 (C-2), 103.8 (C-6), 117.3 (C-8), 119.3 (CN), 121.1 (C-4), 122.6 (C-4a), 130.1 (C-5), 132.0 (C-3), 133.3 (C-7), 156.8 (C-8a) |
| **9e** | 0.92 (d, 6H, 2 × $CH_3$), 0.98 (d, 6H, 2 × $CH_3$), 2.01 (spt, 2H, 2 × CH), 5.46 (d, 1H, $J$ = 10.4, H-3), 6.43 (d, 1H, $J$ = 10.4, H-4), 6.71 (d, 1H, $J$ = 8.5, H-8), 7.14 (d, 1H, $J$ = 1.9, H-5), 7.32 (dd, 1H, $J$ = 1.9, 8.5, H-7) | 16.2 (2 × $CH_3$), 16.9 (2 × $CH_3$), 35.4 (2 × CH), 88.7 (C-2), 102.6 (C-6), 115.4 (C-8), 119.4 (CN), 120.9 (C-4a), 123.2 (C-4), 125.8 (C-3), 130.2 (C-5), 133.5 (C-7), 159.2 (C-8a) |

[a] Satisfactory microanalyses were obtained for all new compounds: C ± 0.3, H ± 0.3.

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