Journal of Organometallic Chemistry, 379 (1989) 81–88
Elsevier Sequoia S.A., Lausanne – Printed in The Netherlands
JOM 20327

Stereoselective synthesis of *cis*-1,3-disubstituted 1,3-dihydroisobenzofurans via arenechromium tricarbonyl methodology

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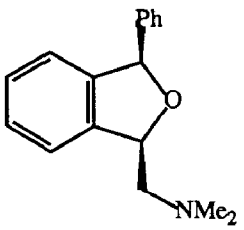
(Received July 23rd, 1989)

Abstract

Phthalanchromium tricarbonyl is converted by t-butyllithium and alkyl halides completely stereoselectively into the corresponding *exo*-1-methyl, ethyl and benzyl derivatives. Double methylation of phthalanchromium tricarbonyl generates completely stereoselectively *exo-cis*-1,3-dimethylphthalanchromium tricarbonyl, from which *cis*-1,3-dimethylphthalan is liberated on oxidation. In contrast, double methylation of phthalan itself produces a 40/60 mixture of *cis*- and *trans*-1,3-dimethylphthalan.

Introduction

Substituted 1,3-dihydroisobenzofurans (phthalans) are of interest owing to their spectroscopic and pharmacological properties [1,2]. Saxena has shown that both the *cis*- and *trans*-isomers of 1-*N*,*N*-dimethylaminomethyl-3-phenylphthalan (**1** and **2**) exhibit antihistaminic activity [3]. The individual diastereoisomers **1** and **2** were obtained following separation of their nitro precursors by fractional recrystallisation; the stereochemical assignments were established by a single crystal X-ray study of the *trans*-isomer **3** of the precursor [4].



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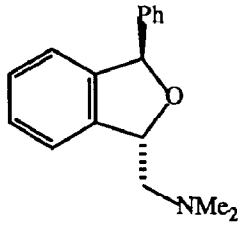

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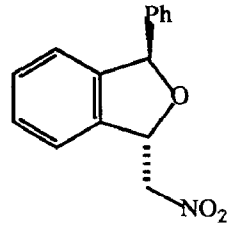

3

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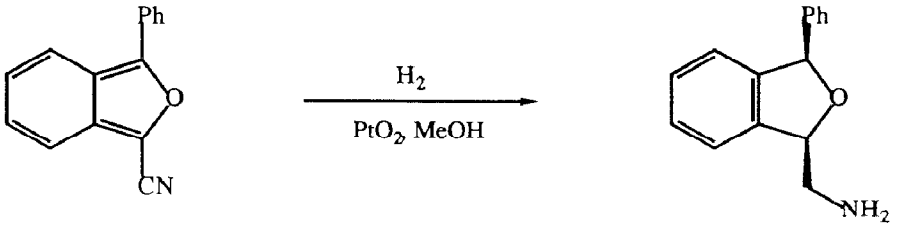
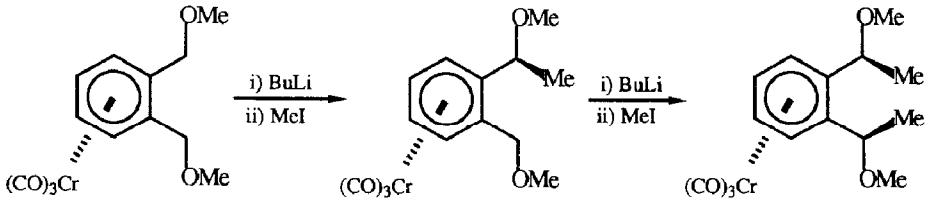
A stereoselective synthesis of *cis*-1,3-disubstituted phthalans has been reported, and involves the hydrogenation of 1-cyano-3-phenylisobenzofuran (**4**), which yields only the *cis*-isomer **5** [4].



4 **5**

We have previously demonstrated the utility of the chromium tricarbonyl moiety for promoting stereoselective benzylic alkylations [5–7]. Thus, double benzylic methylation of the dimethyl-*o*-xylenediyl ether complex **6** gave completely stereoselectively the *meso*-derivative **7** [6]. Furthermore, double methylation of the tetrahydroisoquinoline complex **8** gave completely stereoselectively the *exo-cis*-1,4-dimethyl derivative **9** [7].



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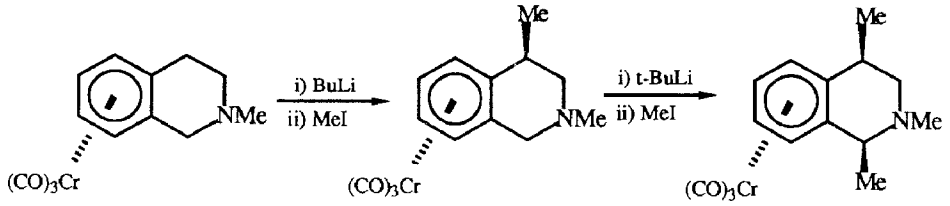
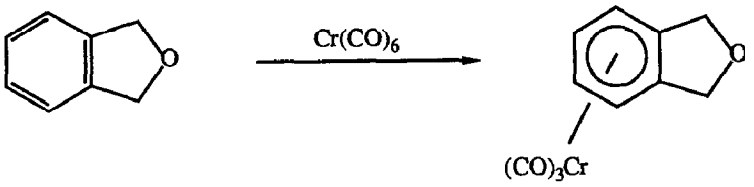


8 **9**

We describe below the application of chromium tricarbonyl methodology to the synthesis of *cis*-1,3-disubstituted phthalans.

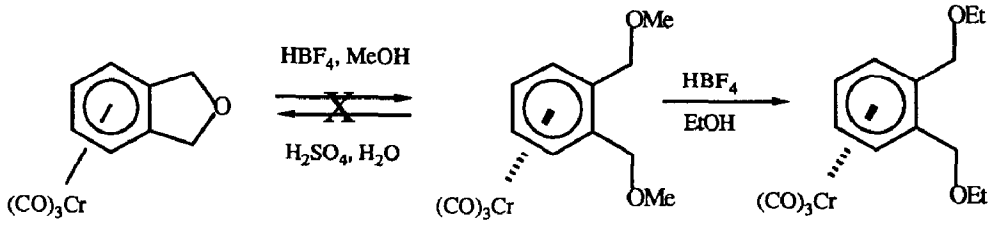
Results and discussion

Thermolysis of chromium hexacarbonyl with phthalan (**10**) under standard conditions [8] gave phthalanchromium tricarbonyl (**11**).



10 11

Treatment of the dimethyl ether complex **6** with aqueous acid produced none of **11** despite ready formation of the benzylic carbonium ion, as evidenced by the trans-etherification of **6** to **12** in acidic ethanol. Furthermore, complex **11** was inert towards acidic methanol, none of complex **6** being detected. The absence of interconversion of **6** and **11** under acidic conditions may be rationalised in stereo-electronic terms. Cyclisation of the chromium tricarbonyl stabilised benzylic carbonium ion [9] derived from **6** would involve an unfavourable 5-*endo-trig* [10] process, while the carbon–oxygen bonds in **11** are unable to adopt the required, antiperiplanar to chromium, conformation for carbonium ion formation.



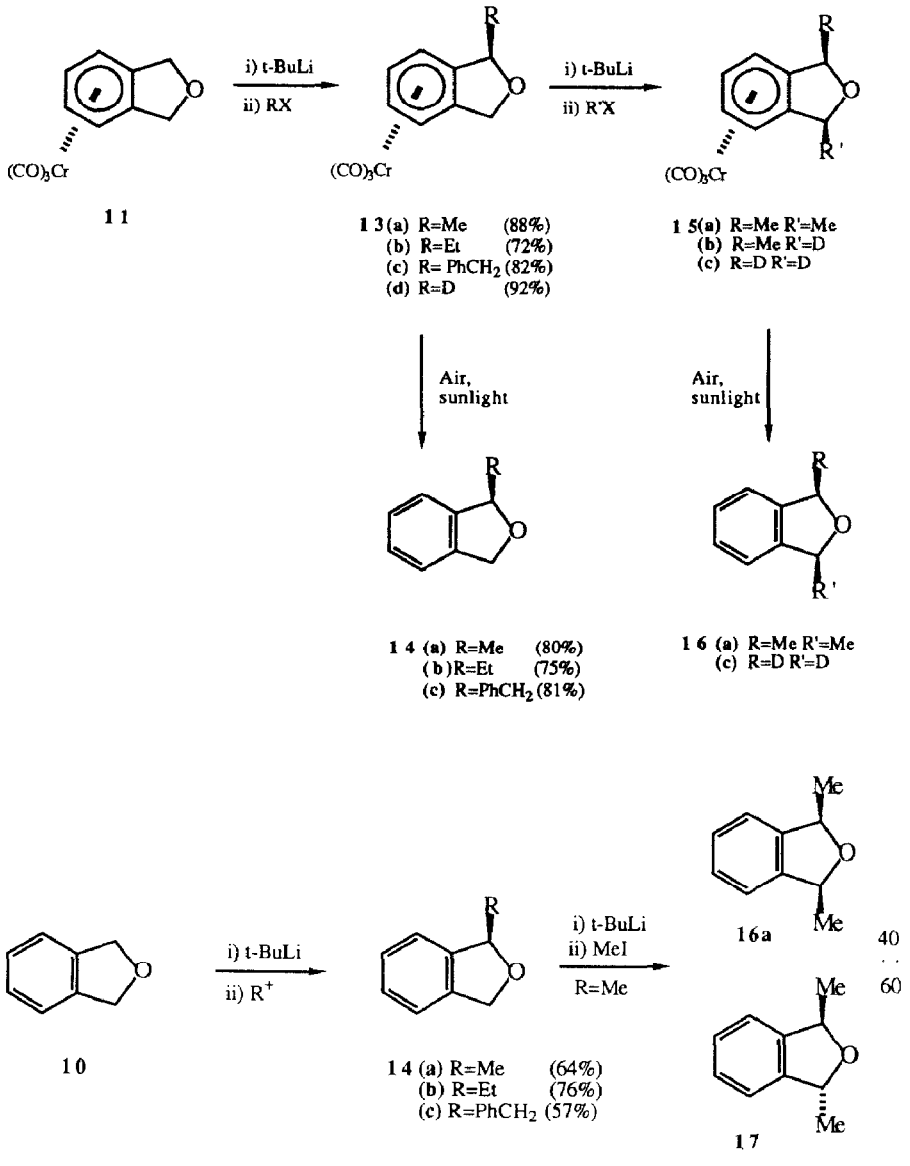
11 6 12

Treatment of **11** with t-butyllithium at −78°C and subsequent addition of methyl iodide gave *exo*-1-methylphthalanchromium tricarbonyl (**13a**) completely stereoselectively in 88% isolated yield. The structure of **13a** was established from its ^{1}H NMR spectrum, the *exo* stereochemistry being assigned by analogy [5–7]. Similarly, ethylation, benzylation and deuteriation of **11** were also completely stereoselective, giving **13b, 13c** and **13d** respectively. Exposure of diethyl ether solutions of complexes **13a–c** to air and sunlight liberated the corresponding 1-alkylphthalans **14a–c** [1,11].

Sequential treatment of complex **13a** with t-butyllithium and methyl iodide gave, completely stereoselectively, *exo-cis*-1,3-dimethylphthalanchromium tricarbonyl (**15a**) as the sole product (91% isolated yield). The structure of **15a** followed from its ^{1}H NMR spectrum, the equivalence of the methyl and benzylic protons confirming the expected *cis* stereochemistry. Oxidative decomplexation of **15a** gave *cis*-1,3-dimethylphthalan (**16a**) [12,13]. Similarly, deuteriation of **13a** with t-butyllithium and deuteriomethanol gave **15b** containing > 90% deuterium in the 3-*exo* position, and none in the 3-*endo* position according to ^{2}H NMR spectroscopy.

Deuteriation of **13d** gave stereoselectively **15c** containing 1.65 deuterium equivalents. This is consistent with a kinetic isotope effect of ca. 2 for the removal of the 3-*exo* proton compared with that of the 1-*exo* deuteron in **13d**. Decomplexation of **15c** gave **16c**.

Direct alkylation of phthalan **10** may also be achieved, although deprotonation proved to be considerably slower than for the complex **11**. Thus exposure of **10** to



t-butyllithium at −78 °C for 6 h gave, after addition of the appropriate alkyl halide, 1-alkylphthalans **14a–c** in good yields. Treatment of 1-methylphthalan (**14a**) with t-butyllithium followed by methyl iodide gave a 40/60 mixture of *cis*- and *trans*-1,3-dimethylphthalan (**16a** and **17**, respectively) with the expected *trans*-isomer predominating [14].

Experimental

All preparations, purification, and reactions of tricarbonyl(η^6-arene)chromium(0) complexes were performed under nitrogen by standard vacuum line techniques.

THF was distilled from sodium benzophenone ketyl under nitrogen. Dibutyl ether was dried over sodium and distilled prior to use. t-Butyllithium was used as a 2.62 *M* solution in pentane. Both IR and ^{2}H NMR spectra were obtained as chloroform solutions. The ^{1}H and ^{13}C NMR spectra were recorded with [^{2}H]chloroform solutions at 300 MHz and 62.9 MHz respectively.

Tricarbonyl(η^6-1,3-dihydroisobenzofuran)chromium(0) ***(11)***

A deoxygenated mixture of 1,3-dihydroisobenzofuran (1.50 g, 12.5 mmol) and hexacarbonylchromium (3.0 g, 13.6 mmol) in dibutyl ether (40 ml) and THF (4 ml) was heated under reflux under nitrogen a (16 h). The cooled solution was filtered and evaporated. The residue was subjected to column chromatography (Al_2O_3 Grade V, Et_2O) and gave a single fraction as a yellow solid. Recrystallisation from Et_2O/hexane gave the *title compound* as yellow needles (2.04 g, 64%), $\nu_{max.}$ 1970 and 1890 cm^{-1} (C=O); δ(H) 5.53–5.25 (4H, m, aromatic protons), 4.93, 4.88 (4H, AB system J_{AB} 10.8 Hz, ArCH_2); *m/z* 256 (*M*$^+$) (Found: C, 51.4; H, 3.2. $C_{11}H_8CrO_4$ calc: C, 51.6; H, 3.15%).

Tricarbonyl(η^6-exo-1-methyl-1,3-dihydroisobenzofuran)chromium(0) ***(13a)***

To a stirred solution of tricarbonyl(η^6-1,3-dihydroisobenzofuran)chromium(0) (**11**) (0.163 g, 0.64 mmol) in THF (20 ml) at −78°C was added t-butyllithium (0.25 ml, 0.66 mmol), and the resulting red solution stirred (−78°C, 1.75 h). Methyl iodide (1 ml, 16.1 mmol) was added and stirring continued −78°C, 2 h). After addition of methanol (1 ml) the mixture was warmed and evaporated. Column chromatography (Al_2O_3 Grade V, Et_2O) gave a single fraction as a yellow oil (0.151 g, 88%). Crystallisation from n-pentane (−20°C) gave the *title compound* as fine yellow needles, $\nu_{max.}$ 1970, 1880 cm^{-1} (C=O) and 1250 cm^{-1} (C–O); δ(H) 5.52–5.23 (4H, m, aromatic protons), 5.16 (1H, dq, *J* 1.7 and 6.5 Hz, ArC*H*CH$_3$), 4.98, 4.87 (2H, ABX system, J_{AB} 12.3, J_{AX} 1.7 Hz, ArCH_2O), 1.44 (3H, d, *J* 6.6 Hz, CHCH_3); *m/z* 270 (*M*$^+$) (Found: 53.0; H, 3.7. $C_{12}H_{10}CrO_4$ calc: C, 53.3; H, 3.7%).

Tricarbonyl(η^6-exo-1-ethyl-1,3-dihydroisobenzofuran)chromium(0) ***(13b)***

Alkylation as above with ethyl iodide as the electrophile gave the *title compound* as a yellow oil (72%), $\nu_{max.}$ 1960 and 1890 cm^{-1} (C=O); δ(H) 5.51–5.22 (4H, m, aromatic protons), 4.99 (1H, m, ArC*H*Et), 4.97, 4.87 (2H, AB system, J_{AB} 11.4 Hz, ArCH_2O), 1.74 (2H, m, CH$_3$CH_2), 1.00 (3H, t, *J* 7. Hz, CH$_2$CH_3); *m/z* 284 (*M*$^+$) (Found: *M*$^+$, 284.0143. $C_{13}H_{12}CrO_4$ calc: *M*, 284.0141).

Tricarbonyl(η^6-exo-1-benzyl-1,3-dihydroisobenzofuran)chromium(0) ***(13c)***

Alkylation as above with benzyl bromide as the electrophile gave the *title compound* as a yellow oil (82%), $\nu_{max.}$ 1970 and 1880 cm^{-1} (C=O); δ(H) 7.38–7.15 (5H, m, uncomplexed aromatic protons), 5.42–5.07 (5H, m, complexed aromatic protons and ArC*H*CH$_2$Ph), 4.80 (2H, br s, ArCH_2O), 3.49, 3.11 (2H, ABX system, J_{AB} 14.0, J_{AX} 7.0, J_{BX} 5.9 Hz, PhCH_2CH); *m/z* 346 (*M*$^+$) (Found: *M*$^+$, 346.0293. $C_{18}H_{14}CrO_4$ calc: *M*, 346.0297).

Tricarbonyl(η^6-exo-1-deuterio-1,3-dihydroisobenzofuran)chromium(0) ***(13d)***

Reaction as above with deuteriomethanol as the electrophile gave the *title compound* as a yellow oil (92%), δ(H) 5.53–5.24 (4H, m, aromatic protons),

5.95–5.85 (3H, m, ArCH_2OCHD); δ(D) 4.93 (1D, br s, ArCHD); *m/z* 257 (M^+).

*Tricarbonyl(η⁶-exo-1,3-dihydroisobenzofuran)chromium(0) (**15a**)*

A solution of tricarbonyl(η⁶-*exo*-1-methyl-1,3-dihydroisobenzofuran)chromium(0) (**13a**) (0.124 g, 0.46 mmol) in THF (20 ml) at −78 °C was treated with t-butyllithium (0.2 ml, 0.52 mmol) in the above fashion and quenched with methyl iodide to give, after chromatography, a yellow oil that solidified on standing (0.118 g, 91%). Recystallisation from Et_2O/pentane afforded the *title compound* as yellow plates, $\nu_{max.}$ 1970 and 1880 cm^{-1} (C=O); δ(H) 5.46–5.25 (4H, m, aromatic protons), 5.13 (2H, q, *J* 6.5 Hz, ArCHCH_3), 1.49 (6H, d, *J* 6.5 Hz, ArCHCH_3); *m/z* 284 (M^+) (Found: C, 55.0; H, 4.1. $C_{13}H_{12}CrO_4$ calc: C, 54.9; H, 4.3%).

*Tricarbonyl(η⁶-exo-1-methyl-3-deuterio-1,3-dihydroisobenzofuran)chromium(0) (**15b**)*

Reaction as above with deuteriomethanol as the electrophile gave the *title compound* as a yellow oil (93%), δ(H) 5.53–5.23 (4H, m, aromatic protons), 5.14 (1H, q, *J* 6.5 Hz, ArCHCH_3), 4.82 (1H, br s, ArCHD), 1.43 (3H, d, *J* 6.5 Hz, ArCHCH_3); Δ(D) 5.53 (1D, br s, ArCHD); *m/z* 271 (M^+). Integration of the molecular ion peak (M^+ 271) with respect to that of complex **13a** revealed ca. 95% deuterium incorporation.

*Tricarbonyl(η⁶-exo-1,3-dideuterio-1,3-dihydroisobenzofuran)chromium(0) (**15c**)*

A solution of tricarbonyl(η⁶-*exo*-1-deuterio-1,3-dihydroisobenzofuran)chromium(0) (**13d**) (0.028 g, 0.11 mmol) in THF (15 ml) at −78 °C was metallated with t-butyllithium (0.07 ml, 0.18 mmol), and the mixture then treated with deuteriomethanol. Column chromatography (Al_2O_3 Grade V, Et_2O) gave the *title compound* as a yellow solid (0.026 g, 92%), δ(H) 5.53–5.25 (4H, m, aromatic protons), 4.86 (2H, br s, ArCHD); δ(D) 4.93 (2D, br s, ArCHD); *m/z* 258 (M^+). Integration of the ^{1}H NMR signals of the *endo* benzylic protons with respect to those for the *exo* benzylic protons of complex **13d** revealed ca. 82% deuterium incorporation consistent with a kinetic isotope effect of ca. 2 for the preferential removal of the 3-*exo* proton over the 1-*exo*-deuteron in complex **13d**.

*General procedure of the decomplexation of the complexes **13a–c**, **15a** and **15c***

A solution of the relevant tricarbonylchromium complex **13a–c**, **15a** or **15c** in Et_2O (20 mg ml^{-1}) was allowed to stand in air and sunlight until the yellow solution became colourless. Filtration (Celite) and evaporation gave the crude decomplexed 1,3-dihydroisobenzofurans as colourless oils. Owing to the ready autoxidation of these compounds [11], further purification (where necessary) was achieved by cup distillation under reduced pressure.

*1-Methyl-1,3-dihydroisobenzofuran (**14a**) [1,11,13].* δ(H) 7.32–7.16 (4H, aromatic protons), 5.34 (1H, dq, *J* 6.4 and 1.8 Hz, ArCHCH_3), 5.15, 5.06 (2H, ABX system, J_{AB} 12.2, J_{AX} 2.2, J_{BX} 1.7 Hz, ArCH_2O), 1.52 (3H, d, *J* 6.1 Hz, ArCHCH_3); *m/z* ($M^+ - 1$).

*1-Ethyl-1,3-dihydroisobenzofuran (**14b**).* $\nu_{max.}$ 1260 cm^{-1} (C–o); δ(H) 7.29–7.16 (4H, m, aromatic protons), 5.22 (1H, br s, ArCHEt), 5.14, 5.08 (2H, ABX system, J_{AB} 12.1, J_{AX} 2.5, J_{BX} 1.3 Hz, ArCH_2O), 1.99–1.71 (2H, m, CH_2CH_3), 0.99 (3H, t, *J* 7.4 Hz, CH_2CH_3); δ(C) 141.97, 139.65, 127.29, 127.14, 121.14, 120.90, 85.02, 72.59, 29.01, 9.16; *m/z* 147 ($M^+ - 1$) (Found: C, 80.95; H, 9.6. $C_{10}H_{12}O$ calc: C, 81.0; H, 8.2%).

*1-Benzyl-1,3-dihydroisobenzofuran (**14c**).* $\nu_{max.}$ 1255 cm^{-1} (C–O); δ(H) 7.43–7.05 (9H, m, aromatic protons), 5.55 (1H, br s, ArC*H*CH_2Ph), 5.09 (2H, br s, ArCH_2O), 5.14 (2H, m, PhCH_2CH); δ(C) 141.47, 139.43, 137.72, 129.52, 128.31, 128.17, 128.05, 127.34, 126.87, 126.17, 121.40, 120.76, 84.32, 72.34, 42.68; *m/z* 209 ($M^+ - 1$) (Found: C, 85.8; H, 7.1. $C_{15}H_{14}O$ calc: C, 85.7; H, 6.7%).

*cis-1,3-Dimethyl-1,3-dihydroisobenzofuran (**16a**) [12,13].* δ(H) 7.30–7.13 (4H, m, aromatic protons), 5.23 (2H, q, *J* 6.2 Hz, ArC*H*CH_3), 1.54 (6H, d, *J* 6.3 Hz, ArCHCH_3); *m/z* 147 ($M^+ - 1$).

*cis-1,3-Dideuterio-1,3-dihydroisobenzofuran (**16c**).* δ(H) 7.32–7.30 (4H, br s, aromatic protons), 5.16 (2H, br s, ArC*H*D).

*General procedure for the alkylation of 1,3-dihydroisobenzofuran (**10**)*

A stirred solution of 1,3-dihydroisobenzofuran (**10**) (1.44 g, 11.9 mmol) in THF (30 ml) at −78°C under nitrogen was treated with t-butyllithium (4.8 ml, 12.6 mmol), to give a red colouration that darkened with time. The mixture was stirred (−78°C, 6 h) and treated with methyl iodide (2 ml, 32.1 mmol), resulting in immediate discharge of the colour. Stirring was continued (−78°C, 1.6 h), methanol (10 ml) was added, and the solution stirred (20°C, 12 h). The solvent was removed, water (40 ml) added and the aqueous layer extracted (Et_2O, 3 × 40 ml). The combined extracts were dried ($MgSO_4$), filtered, and evaporated to give 1-methyl-1,3-dihydroisobenzofuran (**14a**) as a pale brown oil that darkened upon prolonged exposure to air (1.02 g, 64%) [13]. Use of ethyl iodide as the electrophile yielded 1-ethyl-1,3-dihydroisobenzofuran (**14b**) as a colourless oil (76%), while that of benzyl bromide afforded 1-benzyl-1,3-dihydroisobenzofuran (**14c**) (57%).

*Methylation of 1-methyl-1,3-dihydroisobenzofuran (**14a**)*

A stirred solution of 1-methyl-1,3-dihydroisobenzofuran (**14a**) (0.129 g, 0.96 mmol) in THF (10 ml) at −78°C under nitrogen was treated with t-butyllithium (0.4 ml, 1.05 mmol). The mixture was stirred (−78°C, 4.3 h) and treated with methyl iodide (0.5 ml, 8.05 mmol), resulting in discharge of the colour. Stirring was continued (−78°C, 1 h) and the reaction quenched by the addition of methanol (5 ml). The solution was stirred (20°C, 12 h) and concentrated, and water (15 ml), was added. The aqueous layer was extracted (Et_2O, 3 × 10 ml) and the combined extracts were dried ($MgSO_4$). Filtration and evaporation gave a pale yellow oil (0.105 g, 74%). The ^1H NMR spectrum of the product revealed the presence of both *cis-* and *trans*-1,3-dimethyl-1,3-dihydroisobenzofuran (**16a** and **17** respectively) [12,13] in the ratio 1/1.4. δ(H) (*trans* **17**) 7.30–7.14 (4H, m, aromatic protons), 5.41 (2H, q, *J* 5.7 Hz, ArC*H*CH_3), 1.48 (3H, d, *J* 6.2 Hz, ArCHCH_3); *m/z* 166 ($M^+ + 18$).

Acknowledgements

We thank Glaxo Group Research for a studentship (to SJC).

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