Facile Addition of Methyl Lithium to a 4-Vinylpyridine System

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The rapid addition of methyl lithium to the 4-vinylpyridine system present in 4-{2,6-dihydroxy-4-(3-methyl-2-octyl)phenyl}-2-methyl-4-(4-pyridyl)but-3-en-2-ol (**2**) is reported. The α and β-4-{2,6-dihydroxy-4-(3-methyl-2-octyl)phenyl}-2,3-dimethyl-4-(4-pyridyl)butan-2-ols **4** and **5** formed, are cyclised by heating with 5*N* hydrochloric acid to *trans* and *cis*-3,4-dihydro-5-hydroxy-7-(3-methyl-2-octyl)-4-(4-pyridyl)-2,2,3-trimethyl-2*H*-1-benzopyran **6** and **7** respectively.

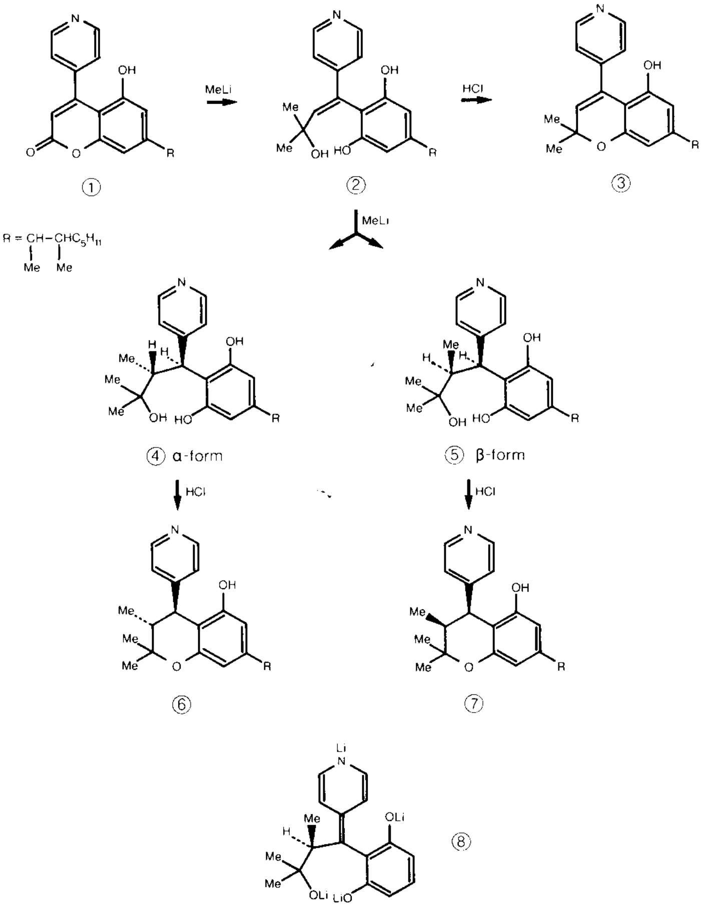
J. Heterocyclic Chem., **21**, 1025 (1984).

2,2-Dimethyl-5-hydroxy-7-(3-methyl-2-octyl)-4-(4-pyridyl)-2*H*-1-benzopyran (**3**, BRL 4664, nonabine) is a new antinauseant drug useful in the treatment of cytotoxic drug induced nausea and vomiting. During its preparation by reaction of the benzopyranone **1** with excess methyl lithium in diethyl ether and cyclisation of the intermediate butenol **2** with dilute hydrochloric acid, varying amounts of impurities including the trimethylbenzopyrans **6** and **7** are formed depending on the temperature of reaction. Razdan *et al.*, [1] reported the preparation of *trans*-3,4-dihydro-5-hydroxy-7-(3-methyl-2-octyl)-4-(4-pyridyl)-2,2,3-trimethyl-2*H*-1-benzopyran (**6**) in about 20% yield by treatment of the benzopyranone **1** or the butenol **2** with excess methyl magnesium bromide in anisole at 100° for 48 hours. A similar result was claimed when the benzopyranone **1** was reacted with methyl lithium in ether, but no details were given.

During investigations into the formation of the trimethylbenzopyrans, it was observed that treatment of the butenol **2** with excess methyl lithium in diethyl ether/tetrahydrofuran for four hours at 20° gave a quantitative yield of a mixture of butanols **4** and **5** formed by addition of methyl lithium to the vinyl pyridine system of the butenol. These were readily separated by column chromatography on silica gel using ethyl acetate as eluent, to give 37% of the α-butanol **4** and 40% of the more polar β-butanol **5**. The nmr spectra of the two compounds were identical apart from very minor chemical shift differences and, in particular, the proton at the 4-position of the butanol chain appeared as a doublet at about δ 4.5 (J = 10 Hz).

Cyclisation of the butanols **4** and **5** was effected by refluxing them with 5*N* hydrochloric acid for 10 minutes to give the isomeric 3,4-*trans*-(**6**) and 3,4-*cis*-(**7**) dihydrobenzopyrans respectively in high yields. Structures were assigned by nmr spectroscopy, when the spectrum of dihydrobenzopyran **6** was identical with that of material previously prepared by Razdan's method [4 position proton signal is a doublet, δ 3.46 (J = 11 Hz)]. The nmr spectrum of the dihydrobenzopyran **7** was very similar to that of its isomer **6** but the 4-position proton signal appeared as a doublet at δ 4.26 (J = 5 Hz). The upfield shift of the 4-position proton in the *trans*-isomer **6** is probably due to the shielding effect of the adjacent methyl group. With the structures of the dihydrobenzopyrans **6** and **7** assigned, the relative configurations of the α and β-butanols **4** and **5** are also determined.

Scheme



Although Razdan *et al.* showed that the 3-methyl group in dihydrobenzopyran **6** is introduced by reaction of methyl magnesium bromide with the butenol **2** prior to cyclisation, the low yield of compound **6** and the rather severe conditions of its formation emphasise the difficulty of carrying out the reaction. The present work shows that in the case of methyl lithium, addition to the 4-vinylpyridine system in the butenol **2** is a rather easy reaction, substantially quantitative under mild conditions. As would be expected from the intermediacy in the reaction of species such as for example, **8**, the α and β-butanols are formed in essentially equal proportions. Cyclisation of the butanols is then a simple matter to give excellent yields of the *trans*- and *cis*-dihydrobenzopyrans **6** and **7**.

It has been reported that 2-vinylpyridine polymerises readily in the presence of Grignard reagents [2,3] and also in the presence of lithium compounds such as butyl lithium or lithium amide derivatives [2]. 2-Styrylpyridine will react cleanly with allyl magnesium bromide but 4-styrylpyridine is more reactive and leads to oligomeric or polymeric products [4]. In the present work, there was no evidence of any polymerisation and presumably, this is because the butenol **2** represents a hindered system towards polymerisation, and the alkyl addition can therefore take place. In support of this, it has been reported by Konakahara and Tagaki [5] that 2-(cyclohexylidenemethyl)pyridine survives treatment with lithium diethylamide in tetrahydrofuran up to room temperature without polymerisation, the major product on quenching being the isomeric compound 1-(2-pyridylmethyl)-1-cyclohexene.

EXPERIMENTAL

The ^{1}H-nmr spectra were recorded on a Perkin Elmer R 12A spectrometer in deuterated dimethyl sulphoxide. Chemical shifts are reported in ppm from TMS as an internal standard and are given in δ units. Elemental analyses were performed by the Physical and Analytical Services Unit. Melting points were determined on a Büchi melting point apparatus and are uncorrected. The tlc samples were run on silica gel, developed with ethyl acetate and detected with a 0.5% solution of fast blue 'B' in 50% aqueous ethanol.

4-{2,6-Dihydroxy-4-(3-methyl-2-octyl)phenyl}-2-methyl-4-(4-pyridyl)but-3-en-2-ol (**2**).

Methyl magnesium iodide was prepared from 147 g (1.04 moles) of methyl iodide and 24.3 g (1.0 g-atom) of magnesium in 900 ml of anhydrous ether. To the stirred Grignard solution was added 55.5 g (0.152 mole) of 5-hydroxy-7-(3-methyl-2-octyl)-4-(4-pyridyl)-2*H*-1-benzopyran-2-one (**1**) [1], portionwise over 0.5 hours, keeping the temperature between 15° and 20°. Stirring was continued for a further 0.75 hour. After standing overnight, the reaction mixture was decomposed by addition to ice cold ammonium chloride solution. The ether layer was separated and the aqueous layer extracted with 2 × 250 ml of ether. The combined ether solutions were washed with 500 ml of water and dried over magnesium sulphate. After treatment with charcoal, the ether solution was filtered and evaporated under reduced pressure to give an oily solid which solidified on drying *in vacuo* to give 57.8 g (0.145 mole, 95%) of the butenol **2**; nmr: δ 0.6-3.0 (m, 19, aliphatic H, plus s, 6, *gem*-dimethyl H at 1.13), 4.62 (broad s, 1, OH), 6.22 (s, 2, aromatic H), 6.52 (s, 1, olefinic H), 7.17 (d, 2, pyridyl H), 8.41 (d, 2, pyridyl H), 8.91 (broad s, 2, phenolic OH). The tlc showed the material to be substantially pure.

Anal. Calcd. for $C_{25}H_{35}NO_3$: C, 75.53; H, 8.87; N, 3.52. Found: C, 75.26; H, 8.98; N, 3.12.

α- and β-4-{2,6-Dihydroxy-4-(3-methyl-2-octyl)phenyl}-2,3-dimethyl-4-(4-pyridyl)butan-2-ol (**4**) and (**5**).

To a stirred solution of 5.5 g (0.25 mole) of methyl lithium in 230 ml of ether under nitrogen, was added 12.0 g (0.03 mole) of the butenol **2** over 40 minutes at a temperature of 5°-10°. Stirring was continued for a further 4 hours at 20°. After cooling to about 5°, the reaction mixture was decomposed by addition of 100 ml of water over 25 minutes, and the ether layer was washed with water to *p*H 8 followed by drying over anhydrous sodium sulphate. Removal of solvent under reduced pressure gave 12.74 g (quantitative yield) of a solid foam. The tlc showed this to consist of two major components in approximately equal proportions with only traces of impurities present. Column chromatography of 11.22 g (0.027 mole) of the foam (silica gel/ethyl acetate), using slight pressure, effected a clean separation to give 4.18 g (37%) of the α-butanol **4** and 4.51 g (40%) of the more polar β-butanol **5** isolated as solid foams. The tlc showed these materials to be substantially pure, but analysis indicated the retention of about 4% ethyl acetate.

α-Butanol **4**.

This compound had nmr: δ 0.55-3.15 (m, 23, aliphatic H, plus s, 6, *gem*-dimethyl H at 1.05), 3.88 (broad s, 1, OH), 4.41 (d, 1, J = 10 Hz, H-4), 6.11 (s, 2, aromatic H), 7.4 (d, 2, pyridyl H), 8.36 (d, 2, pyridyl H), 9.15 (s, 2, phenolic OH).

Anal. Calcd. for $C_{26}H_{39}NO_3$ (plus 4% $C_4H_8O_2$): C, 74.66; H, 9.49; N, 3.25. Found: C, 74.67; H, 9.33; N, 3.07.

β-Butanol **5**.

This compound had nmr: δ 0.55-3.1 (m, 23, aliphatic H, plus s, 6, *gem*-dimethyl H at 1.02), 3.87 (broad s, 1, OH), 4.53 (d, 1, J = 10 Hz, H-4), 6.05 (s, 2, aromatic H), 7.45 (d, 2, pyridyl H), 8.28 (d, 2, pyridyl H), 8.99 (s, 2, phenolic OH).

Anal. Calcd. for $C_{26}H_{39}NO_3$ (plus 4% $C_4H_8O_2$): C, 74.66; H, 9.49; N, 3.25. Found: C, 74.82; H, 9.57; N, 2.88.

trans-3,4-Dihydro-5-hydroxy-7-(3-methyl-2-octyl)-4-(4-pyridyl)-2,2,3-trimethyl-2*H*-1-benzopyran (**6**).

A solution of 3.34 g (0.0081 mole) of the α-butanol **4** in 20 ml of ether was added to 50 ml of 5*N* hydrochloric acid and the ether allowed to evaporate. The residual mixture was refluxed for 10 minutes at about 105° with vigorous stirring and was then cooled to room temperature and basified with 10% aqueous sodium hydroxide solution. The residue was extracted with ether and the ether solution dried over anhydrous sodium sulphate. Removal of solvent gave 3.0 g (0.0076 mole, 94%) of the *trans*-dihydrobenzopyran **6** as a solid foam which showed a single spot on tlc. Crystallisation of 2.67 g of this material from ethanol/acetonitrile gave 1.10 g of solid **6**, mp 189-191° (lit [1], mp 193-195° ex acetonitrile); nmr: δ 0.5-3.0 (m, 23, aliphatic H, plus s, 6, *gem*-dimethyl H at 1.09), 3.46 (d, 1, J = 11 Hz, H-4), 6.07 (d, 2, aromatic H), 7.04 (d, 2, pyridyl H), 8.35 (d, 2, pyridyl H), 8.80 (s, 1, phenolic OH).

Anal. Calcd. for $C_{26}H_{37}NO_2$: C, 78.94; H, 9.43; N, 3.54. Found: C, 79.17; H, 9.54; N, 3.32.

cis-3,4-Dihydro-5-hydroxy-7-(3-methyl-2-octyl)-4-(4-pyridyl)-2,2,3-trimethyl-2*H*-1-benzopyran (**7**).

This compound was prepared from 2.86 g (0.0069 mole) of the β-butanol **5** in 60 ml of ether and 50 ml of 5*N* hydrochloric acid as described above. Work up gave 2.46 g (0.0062 mole, 90%) of the *cis*-dihydrobenzopyran **7** as a solid foam which showed a single spot on tlc. This material was further chromatographed (silcia gel/ethyl acetate) to give after evaporation, 2.34 g (95% recovery) of **7**, again as a solid foam; nmr: δ 0.52-3.0 (m, 23, aliphatic H, plus s, 6, *gem*-dimethyl H at 1.08), 4.26 (d, 1, J = 6 Hz, H-4), 6.16 (broad s, 2, aromatic H), 7.04 (d, 2, pyridyl H), 8.39 (d, 2, pyridyl H), 8.96 (s, 1, phenolic OH).

Anal. Calcd. for $C_{26}H_{37}NO_2$: C, 78.94; H, 9.43; N, 3.54. Found: C, 78.68; H, 9.47; N, 3.20.

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