The Synthesis of 4(6)-t-Butylpyrimidines from 4(6)-Halopyrimidines by Using Higher-Order Lithium and Magnesium Organocuprate Reagents

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Abstract

t-Butyllithium and t-butylmagnesium chloride cyanocuprates were used to prepare 4(6)-t-buty1pyrimidines from the corresponding 4(6)-halopyrimidines. The highly hindered 2,4,5-tri-t-butyl-6-chloropyrimidine, containing an ortho-di-t-butyl arrangement, was prepared by this method. No alkyl group isomerization was observed but some substrate reduction was detected.

Introduction

In 1972, two research groups disclosed an efficient method for selective carbon-carbon bond formation by nickel complex-catalysed cross-coupling of Grignard reagents with aryl halides. Tamao, Sumitani and Kumada showed that even Grignard reagents containing β-hydrogen atoms, reagents which are commonly unstable, may be used. Although this method has been applied extensively to prepare 4(6)-alkylpyrimidines, subsequent experiments by Kumada showed that secondary and (to a greater extent) tertiary alkyl Grignard reagents undergo extensive alkyl group isomerization to produce primary alkyl groups. In addition, these reagents often caused unwanted reduction of the halide.

Many so-called general methods of substituting an alkyl group for a halide suffer in this way. Reactions that go smoothly with primary alkyl carbon nucleophiles are often less successful with secondary and tertiary alkyl carbon nucleophiles due to the greater chance of isomerization and β elimination. Because of our interest in pyrimidines bearing t-butyl groups in the 4 and 6 positions, we investigated alternative organometallic reactions in an effort to obtain high yields of substitution products and avoid both alkyl group isomerization and substrate reduction.

Results and Discussion

A recent upsurge in the use of so-called higher order mixed organocuprates (general formula $R_n R'CuLi_n$, $n \geq 2$) prompted us to make use of these reagents.

Tertiary higher-order organocuprate reagents have been shown to be highly reactive towards unactivated alkyl halides and, more importantly, display little tendency to isomerize. Thus, in a series of reactions, substituted 4-chloro- and 4-iodo-pyrimidine compounds were treated with the mixed higher-order organocuprate formed by adding 2 equiv. of t-butyllithium or t-butylmagnesium chloride to 1 equiv. of copper(I) cyanide (Table 1).

Table 1. Conversion of 4(6)-halopyrimidine derivatives (1) into 4(6)-t-butylpyrimidine derivatives (2)

<table>
<thead>
<tr>
<th>Compound series</th>
<th>Substrate (1)</th>
<th>Gegenion</th>
<th>Yield of (2) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) H H Bu^t</td>
<td>Li</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>(b) H H Bu^t</td>
<td>Li</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>(c) Bu^t H Bu^t</td>
<td>Li</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>(d) Bu^t H Bu^t</td>
<td>Li</td>
<td>85</td>
<td></td>
</tr>
<tr>
<td>(e) Bu^t Br Bu^t</td>
<td>Li</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>(f) Me H Bu^t</td>
<td>Li</td>
<td>78</td>
<td></td>
</tr>
<tr>
<td>(g) Me Br Bu^t</td>
<td>Li</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>(h) Me PhCH_2O H</td>
<td>Li</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>(i) Bu^t Bu^t</td>
<td>Cl Cl MgCl</td>
<td>25</td>
<td></td>
</tr>
</tbody>
</table>

It is interesting to note that 4(6)-iodopyrimidines gave high yields of substituted products whereas the chloro analogues were recovered unreacted (Table 1). The observed higher reactivity of iodo compounds has been noted previously and was clearly demonstrated when we treated a 4:1 mixture of 4-t-butyl-6-iodopyrimidine (1b) and 4-t-butyl-6-chloropyrimidine (1a) (by g.l.c. analysis) with the higher-order organocuprate. Analysis of the product mixture revealed a 4:1 mixture of 4,6-di-t-butylpyrimidine (2b) and unreacted 4-t-butyl-6-chloropyrimidine, respectively. No unreacted iodo compound could be detected.

The synthetic utility of this reaction is enhanced by the observation that a 5-bromo substituent is left untouched while the halogen next to it is displaced. This presumably reflects the higher electron density on C5 of the pyrimidine ring. The diminished yields in this case may be attributed to the steric repulsions encountered between the large bromo substituent and the nucleophile.

This steric hindrance is even more extreme with the 2,5-di-t-butyl-4,6-dihalopyrimidines. In this case the higher-order t-butyllithium organocuprate reagent did not displace either chloride or iodide. In the former, no reaction occurred and in the latter only products due to substrate reduction were detected.

Recently Bell, Hu and Patel\textsuperscript{6} reported that brominated and chlorinated nitrogenous heterocycles could be coupled directly with alkyl organometallic reagents in high yields. They found that 2-halo, 3-halo and 4-halo heterocycles from the pyridine, quinoline and 1,10-phenanthroline series, when treated with a fourfold excess of alkylmagnesium bromide/copper(0) cyanide (2:1) reagent, gave yields from 50 to 75\% of the alkylated product.

We have found that this procedure is also successful, albeit in somewhat lower yields, when applied to sterically hindered chloropyrimidines. When 2,5-di-t-butyl-4,6-dichloropyrimidine (1i) was treated with an eightfold molar excess of the mixed 2:1 t-butylmagnesium chloride/cuprous cyanide reagent, 2,4,5-tri-t-butyl-6-chloropyrimidine (2i) was isolated in a 25\% yield, along with substantial amounts of reduction products.

When 2,4,5-tri-t-butyl-6-chloropyrimidine (2i) was subjected to a second treatment with the mixed organometallic reagent as above, no reaction took place and the starting material was recovered unchanged. This lack of reactivity is presumably due to a combination of steric repulsion between the incoming nucleophile and the t-butyl group adjacent to the chloro substituent, and an increased electron density in the pyrimidine ring. The increased electron density is caused by the replacement of one of the electron-attracting chlorine atoms in 2,5-di-t-butyl-4,6-dichloropyrimidine (1i) by a t-butyl group.

We intend to explore further the application of this direct t-butylation of halogenated pyrimidine compounds, and to extend these results into other heterocyclic systems.

\textbf{Experimental}

All melting points were taken in open capillary tubes in an electrically heated silicone oil bath and are uncorrected. Elemental analyses were performed by the University of Queensland Microanalytical Service, a Carlo Erba Strumentazione 1106 elemental analyser being used. Mass spectra were recorded on a Kratos MS25RFA instrument at 70 eV with an accelerating voltage of 4 kV. \textsuperscript{1}H n.m.r. spectra were measured at 60 MHz with a Varian EM360 instrument. \textsuperscript{13}C n.m.r. spectra were recorded on a Jeol FX-100 spectrometer at 25.1 MHz at concentrations of 80–150 mg/ml in (D)chloroform as solvent and internal lock. Spectra were referenced to tetramethylsilane. All reactions involving organometallic reagents and intermediates were performed under an atmosphere of dry nitrogen. Glassware and syringes for such reactions were dried in an oven overnight at 120° prior to use. Ethereal solvents were freshly distilled from sodium benzophenone ketyl. t-Butyllithium and t-butylmagnesium chloride were purchased from Aldrich Chemical Company, and titrated according to the method of Watson and Eastham.\textsuperscript{7} Analytical g.l.c. was performed on a Hewlett-Packard 5710-A gas chromatograph with a 25 m BP5 capillary column. Preparative g.l.c. was performed on a Shimadzu GC-9A gas chromatograph with a 10\% OV-101 column. Nitrogen was the carrier gas in both cases. Column chromatography was carried out by using silica gel (Kieselgel 60, 230–400 mesh, Merck) as adsorbent and with eluents as stated.

Sodium ethoxide was prepared by dissolving sodium (0.58 g, 25 mmol) in anhydrous ethanol (50 ml). To this were added methyl 4,4-dimethyl-3-oxovalerate (2 g, 12.6 mmol) and acetamidine hydrochloride (1.20 g, 12.6 mmol), and the mixture was stirred at room temperature for 16 h. After this period the ethanol was removed by distillation under reduced pressure, and the solid residue was dissolved in water (50 ml). The aqueous solution was acidified with acetic acid to pH 3 whereupon a precipitate formed which was collected by vacuum filtration. After recrystallization from hexane, 4-t-butyl-2-methylpyrimidin-6-ol (1.7 g, 81%) melted at 135-136° (Found: C, 64.5; H, 8.4; N, 17.0%; M+1, 166.11060. C8H14N2O requires C, 65.0; H, 8.5; N, 16.9%; M+1, 166.11053). A molecular ion at the correct values of m/z 166 was noted in the mass spectrum. 

\[^1H\mathrm{n.m.r.}(\mathrm{CDCl}_3)\]
1.26, s, (CH3)3C; 2.47, s, 2-CH3; 6.37, s, H5.

\[^{13}C\mathrm{n.m.r.}(\mathrm{CDCl}_3)\]
177.75, C4; 166.64, CG; 157.46, C2; 105.80, C5; 37.23, (CH3)3C; 28.63, (CH3)3C; 21.62, 2-CH3.

5-Bromo-4-t-butyl-2-methylpyrimidin-6-ol

To a solution of 4-t-butyl-2-methylpyrimidin-6-ol (2 g, 12 mmol) in acetic acid (50 ml) was added bromine (1.92 g, 12 mmol) in acetic acid (5 ml), and the mixture was stirred at room temperature for 24 h. The resulting precipitate was collected by vacuum filtration and was recrystallized from ethanol to give 5-bromo-4-t-butyl-2-methylpyrimidin-6-ol (2.5 g, 85%) as a white solid with a melting range of 185-192° (dec.) (Found: C, 44.1; H, 5.4; N, 11.2%; M+1, 246.01960. C12H13BrN2O requires C, 44.1; H, 5.3; N, 11.4%; M+1, 246.01913). The mass spectrum showed the expected molecular ion cluster (1:1) at m/z 244 and 246. \[^1H\mathrm{n.m.r.} (\mathrm{CDCl}_3/\mathrm{CD}_3\mathrm{SOCD}_3)\]
1.50, s, (CH3)3C; 1.37, s, (CH3)3C.

\[^{13}C\mathrm{n.m.r.}(\mathrm{CDCl}_3/\mathrm{CD}_3\mathrm{SOCD}_3)\]
170.24, C4; 160.59, C6; 154.59, C2; 109.02, C5; 39.14, (CH3)3C; 28.34, (CH3)3C; 21.03, 2-CH3.

2,5-Di-t-butylpyrimidine-4,6-diol

Sodium ethoxide was prepared by dissolving sodium (5 g, 0.1 mol) in anhydrous ethanol (150 ml). To this were added diethyl t-butylnomalate (20 g, 0.1 mol) and trimethylacetamidine hydrochloride (14 g, 0.1 mol), and the mixture was stirred at room temperature for 10 h, then heated to reflux for 3 h. After this period the ethanol was removed by distillation under reduced pressure, and the solid residue was dissolved in water (50 ml). The aqueous solution was acidified with acetic acid to pH 3 whereupon a precipitate formed which was collected by vacuum filtration. 2,5-Di-t-butylpyrimidine-4,6-diol (18 g, 80%) was recrystallized from aqueous ethanol and did not melt up to 300° (Found: C, 64·3; H, 9·0; N, 12·5%). \[^1H\mathrm{n.m.r.} (\mathrm{CF}_3\mathrm{COOH})\]
1.52, s, (CH3)3C; 1·37, s, (CH3)3C.

\[^{13}C\mathrm{n.m.r.}(\mathrm{CDCl}_3/\mathrm{CD}_3\mathrm{SOCD}_3)\]
170·24, C4; 160·59, C6; 154·59, C2; 109·02, C5; 39·14, (CH3)3C; 28·34, (CH3)3C; 21·03, 2-CH3.

**General Procedure for the Preparation of Chloropyrimidines**

A mixture of the pyrimidinol (2 g), phosphoryl chloride (30 ml) and diethylaniline (2 ml) was refluxed for 6 h during which the evolution of hydrogen chloride was observed. After this period the excess phosphoryl chloride was removed by distillation under reduced pressure, and the resulting dark residue was cautiously poured onto crushed ice (80 g). The ice was allowed to melt and the mixture, made alkaline by the addition of aqueous ammonia, was extracted with hexane (3x80 ml). The combined hydrocarbon extracts were washed with saturated sodium hydrogen carbonate solution, dried (MgSO4), and then concentrated under reduced pressure to give the crude product.

\* The systematic names of the 'pyrimidin-6-ols' require the principal group, named as suffix, to be assigned 'lowest locants' [IUPAC rule C-15.11(b)], e.g. 6-t-butyl-2-methylpyrimidin-4-ol. The locants in this paper have been chosen to emphasize the relation between the pyrimidinols and the chloropyrimidines derived from them.

whereupon a thick precipitate formed. The precipitate was collected by vacuum filtration, iodopyrimidine. In each case the iodopyrimidine was tested for purity by n.m.r., with ether (3x50 ml), and isolated as a white solid. Further purification by distillation (70°/0.2 mmHg) yielded 4-t-butyl-6-chloro-2-methylpyrimidine (1·77 g, 80%) with a melting range of 65-65.2° [Found: C, 58·2; H, 7·1; N, 15·3%; M**, 184·07610. C9H13ClN2 requires C, 58·5; H, 7·1; N, 15·2%; M** (C9H1335ClN2), 184·07665]. A molecular ion cluster in the isotopic ratio of 3:1 was observed at m/z 184 and 186, respectively, in the mass spectrum of this sample. 1H n.m.r. δ (CDCl3) 1·32, s, (CH3)3C; 2·70, s, 2-CH3; 7·13, s, H5. 13C n.m.r. δ (CDCl3) 179-32, C4; 167·80, C2; 160·68, C6; 113·27, C5; 37·25, (CH3)3C; 28·82, (CH3)2C; 25·46, 2-CH3.

5-Bromo-4-t-butyl-6-chloro-2-methylpyrimidine

This compound was prepared from 5-bromo-4-t-butyl-2-methylpyrimidin-6-ol (2 g, 8·2 mmol) and isolated as a pale yellow solid. The crude 5-bromo-4-t-butyl-6-chloro-2-methylpyrimidine was purified by distillation (58°/1·8 mmHg) to yield a white solid (1·81 g, 84%) with a melting range of 52-52.5° [Found: C, 40·8; H, 4·6; N, 10·6%; M**, 261·98279. C9H12BrClN2 requires C, 41·0; H, 4·6; N, 10·6%; M** (C9H1279Br35ClN2), 261·98222] A molecular ion cluster at the correct m/z values of 262, 264 and 266 in the expected isotopic ratio of 3:4:1 was noted in the mass spectrum. 1H n.m.r. δ (CDCl3) 1·50, s, (CH3)3C; 1·37, s, (CH3)3C; 7·05, s, H5. 13C n.m.r. δ (CDCl3) 175·34, C4; 164·75, C2; 161·77, C6; 115·38, C5; 40·43, (CH3)2C; 28·15, (CH3)3C; 25·02, 2-CH3.

2,4-Di-t-butyl-6-chloropyrimidine (1c)

This compound was prepared from 2,4-di-t-butylpyrimidin-6-ol9 (2 g, 9·6 mmol) and isolated as a pale yellow oil. Subsequent distillation (b.p. 110°/9 mmHg) gave 2,4-di-t-butyl-6-chloropyrimidine (1·6 g, 75%) as a clear oil with a g.l.c.-determined purity greater than 99% (Found: M**", 226·1240. C12H19 ClN2 requires M**, 226·1237). 1H n.m.r. δ (CDCl3) 1·30, s, (CH3)3C; 1·37, s, (CH3)3C; 7·05, s, H5. 13C n.m.r. δ (CDCl3) 178·9, C4; 177·5, C2; 161·1, C6; 113·4, C5; 39·7, (CH3)3C; 37·8, (CH3)2C; 29·4, (CH3)3C; 29·2, (CH3)2C.

2,5-Di-t-butyl-4,6-dichloropyrimidine (1f)

This compound was prepared from 2,5-di-t-butylpyrimidine-4,6-diol (2 g, 10 mmol) as a pale yellow oil. The crude product was distilled (b.p. 84°/0·05 mmHg) to give 2,5-di-t-butyl-4,6-dichloropyrimidine (2·1 g, 80%) as an almost colourless oil (Found: C, 55·1; H, 7·0; N, 10·6. C12H19Cl2N2 requires C, 55·2; H, 6·95; N, 10·7%). 1H n.m.r. δ (CDCl3) 1·4-1·8, s, (CH3)3C; 1·7-1·9, s, (CH3)2C. 13C n.m.r. δ (CDCl3) 173·1, C2; 160·4, C4(6); 134·5, C5; 38·5, (CH3)3C; 36·5, (CH3)2C; 31·1, (CH3)2C. This compound readily hydrolysed on standing, depositing a low-melting solid. The solid gave analysis consistent with 2,5-di-t-butyl-6-chloropyrimidine-4-ol (Found: C, 59·4; H, 7·9. C12H19ClN2O requires C, 59·4; H, 7·9%).

General Procedure for the Preparation of Iodopyrimidines

Following the method of Gabriel and Colman10 the chloropyrimidine (8 mmol) was slowly added to a rapidly stirred solution of hydriodic acid (10 ml of 55%), and the mixture was stirred at room temperature for 15 min. The resulting slurry was chilled overnight at 5° whereupon a thick precipitate formed. The precipitate was collected by vacuum filtration, then immediately dissolved in aqueous ammonia (40 ml). The resulting solution was extracted with ether (3x50 ml). The combined ether extracts were washed with 5% sodium metabisulphite solution (2x30 ml), dried (MgSO4), and concentrated under reduced pressure to give the iodopyrimidine. In each case the iodopyrimidine was tested for purity by g.l.c. analysis and n.m.r., and used immediately without further purification to avoid hydrolysis by atmospheric moisture.

4-t-Butyl-6-iodopyrimidine (1b)

This compound was prepared from 4-t-butyl-6-chloropyrimidine (1a), and isolated as a clear oil in 89% yield with a g.l.c.-determined purity of 97%. $^1$H n.m.r. $\delta$ (CDCl$_3$) 1·35, s, (CH$_3$)$_3$C; 7·30, s, H5; 8·95, s, H2.

2,4-Di-t-butyl-6-iodopyrimidine (1d)

This compound was prepared as above from 2,4-di-t-butyl-6-chloropyrimidine, and isolated as a pale yellow oil in 51% yield with a g.l.c.-determined purity of greater than 98%. $^1$H n.m.r. $\delta$ (CDCl$_3$) 1·31, s, (CH$_3$)$_3$C; 1·38, s, (CH$_3$)$_3$C; 7·1, s, H$_5$.

5-Bromo-2,4-di-t-butyl-6-iodopyrimidine (1e)

This compound was prepared from 5-bromo-2,4-di-t-butyl-6-chloropyrimidine as above, and isolated as a pale yellow oil in 62% yield with a g.l.c.-determined purity of 96%. $^1$H n.m.r. $\delta$ (CDCl$_3$) 1·38, s, (CH$_3$)$_3$C; 1·51, s, (CH$_3$)$_3$C.

4-t-Butyl-6-iodo-2-methylpyrimidine (1f)

This compound was prepared from 4-t-butyl-6-chloro-2-methylpyrimidine (1 g, 5·4 mmol). It was isolated as a pale yellow solid (1·30 g, 87%) with a g.l.c. purity of 98%. $^1$H n.m.r. $\delta$ (CDCl$_3$) 1·30, s, (CH$_3$)$_3$C; 2·66, 2-CH$_3$; 7·55, s, H$_5$. $^{13}$C n.m.r. $\delta$ (CDCl$_3$) 177·69, C$_4$; 167·86, C$_2$; 130·06, C$_6$; 124·98, C$_5$; 37·30, (CH$_3$)$_3$C; 29·18, (CH$_3$)$_1$C; 25·85, 2-CH$_3$.

5-Bromo-4-t-butyl-6-iodopyrimidine (1g)

This compound was prepared from 5-bromo-4-t-butyl-6-chloro-2-methylpyrimidine (1 g, 3·80 mmol). It was isolated as a pale yellow solid (0·94 g, 70%) with a g.l.c. purity of 97%. $^1$H n.m.r. $\delta$ (CDCl$_3$) 1·50, s, (CH$_3$)$_3$C; 2·63, s, 2-CH$_3$.

5-Benzylx-4-iodo-2-methylpyrimidine (1h)

This compound was prepared from 5-benzylx-4-chloro-2-methylpyrimidine (1 g, 4·26 mmol). It was isolated as a pale yellow solid (1·05 g, 75%) with a g.l.c. purity of 97%. $^1$H n.m.r. $\delta$ (CDCl$_3$) 2·64, s, 2-CH$_3$; 5·22, s, PhCH$_2$O; 7·35-7·46, m, ArH; 7·92, s, H$_6$.

General Procedure for Bu$_2$Cu(CN)L$_2$ Coupling with 4(6)-Halopyrimidines

Under an atmosphere of dry nitrogen a flask containing copper(i) cyanide (0·5 g, 5·6 mmol) was flame-dried and allowed to cool. The flask was then charged with freshly distilled tetrahydrofuran (30 ml) by syringe, and the stirred mixture was cooled to -78°. To this was added t-butyllithium (10 mmol) in pentane (7 ml), and the mixture was briefly warmed to 0° whereupon the solution went black. This mixture was recooled to -78° and the 4(6)-halopyrimidine (5 mmol) in dry tetrahydrofuran (10 ml) was added. The stirred mixture was allowed to warm to room temperature overnight, and was then stirred for a further 2 days. After this period the black solution was poured into saturated ammonium chloride solution (50 ml), and the resulting mixture was extracted with diethyl ether (3x50 ml). The combined ether extracts were dried (MgSO$_4$) and concentrated under reduced pressure to give the crude product.

4,6-Di-t-butylpyrimidine (2b)

This compound was prepared from 4-t-butyl-6-iodopyrimidine, and purified by distillation (b.p. 70°/5 mmHg, lit.$^{13}$ 101°/13 mmHg) followed by column chromatography (chloroform) to give 4,6-di-t-butylpyrimidine as a clear oil in 90% yield. $^1$H n.m.r. $\delta$ (CDCl$_3$) 1·4, s,
Synthesis of 4(6)-t-Butylpyrimidines

This compound was prepared from 2,4-di-t-butyl-6-iodopyrimidine as above to give a solid which was recrystallized from methanol, and sublimed to give white needles that melted at 80° (lit.14 79-80°) (Found: C, 76.7; H, 11.6; N, 11.1. Calc. for C16H28N2: C, 77.4; H, 11.4; N, 11.3%).

1H n.m.r. δ (CDCl3) 1.3, s, 18H, (CH3)3C; 1.4, s, 2-(CH3)3C; 7.0, s, 9H, H 5.

13C n.m.r. δ (CDCl3) 176.4, C4(6); 174.9, C2; 107.2, C5; 39.5, (CH3)3C; 37.6, (CH3)3C; 29.7, (CH3)3C; 29.6, (CH3)3C.

This compound was prepared as above from 5-bromo-2,4-di-t-butyl-6-iodopyrimidine to give a dark oil which was purified by column chromatography (chloroform) to give 5-bromo-2,4,6-tri-t-butylpyrimidine as a pale yellow oil (Found: C, 58.6; H, 8.4; N, 8.6. C16H27BrN2 requires C, 58.7; H, 8.3; N, 8.6%).

1H n.m.r. δ (CDCl3) 1.3, s, 9H, 2-(CH3)3C; 1.38, s, 18H, 4(6)-(CH3)3C.

5-Benzylxy-4-t-butyl-2-methylpyrimidine (2h)

This compound was prepared from 5-benzyloxy-4-iodo-2-methylpyrimidine (1.63 g, 5 mmol), and recrystallized from water/methanol to yield 5-benzyloxy-4-t-butyl-2-methylpyrimidine with a m.p. of 63° (0-90 g, 70%) (Found: C, 74.6; H, 8.2; N, 10.7%. Calc., 256-15770. C16H20N2O requires C, 75.0; H, 7.9; N, 10.9%. M**, 256-15770). A molecular ion of m/z 256 was noted in the mass spectrum of this compound. 1H n.m.r. δ (CDCl3) 1.40, s, (CH3)3C; 2.64, s, 2-CH3; 5.14, s, CH2O; 7.34, m, CGH~; 8.19, s, HG.

13C n.m.r. δ (CDCl3) 165.20, C2; 158.95, C4; 149.30, C5; 139.65, C6; 135.96, C1 (Ph); 128.95, C4 (Ph); 127.35, C2,6 (Ph); 70-47, ArCH2O; 37-90, (CH3)3C; 28-00, (CH3)2C; 25-04, 2-CH3.

2,4,5-Tri-t-butyl-6-chloropyrimidine (2i)

Copper(i) cyanide (5.34 g, 60 mmol) was added to a solution of t-butylmagnesium chloride (120 mmol) in dry tetrahydrofuran (30 ml) at -78°, and the mixture was stirred under an atmosphere of dry nitrogen for 20 min. After this period a solution of 2,5-di-t-butyl-4,6-dichloropyrimidine (1.96 g, 7.5 mmol) in tetrahydrofuran (20 ml) was added, and a

temperature of -78° was maintained for 2 h. The stirred mixture was then allowed to warm to room temperature overnight. The solution was poured onto aqueous ammonium hydroxide solution (50 ml of 30%), and the organic layer was removed. The aqueous phase was extracted with diethyl ether (3×40 ml), and the combined organic extracts were dried (MgSO₄) and concentrated under reduced pressure to give a multicomponent oil. The oil was separated by column chromatography (chloroform) and further purified by preparative gas chromatography to give 2,4,5-tri-t-butyl-6-chloropyrimidine as a colourless oil (0.53 g, 25%) with a g.l.c.-determined purity greater than 99% (Found: M⁺, 282·1859. C₁₆H₂₇₅Cl₂ requires M⁺, 282·1863). ¹H n.m.r. δ (CDCl₃) 1·35, s, (CH₃)₃C; 1.38, s, (CH₃)₃C; 1·59, s, (CH₃)₃C. ¹³C n.m.r. δ (CDCl₃) 175·5, C 2; 167·7, C 4; 158·6, C 6; 135·2, C 5; 42·9, (CH₃)₃C; 37·8, (CH₃)₃C; 35·9, (CH₃)₃C; 31·9, (CH₃)₃C; 31·6, (CH₃)₃C; 29·0, (CH₃)₃C.

Acknowledgment

We acknowledge the efforts of Dr M. E. Nolan in preparing the first sample of 2,5-di-t-butylpyrimidine-4,6-diol.